A POLICY REPORT ON TUMOUR PROFILING IN SINGAPORE:

OBTAINING INFORMED CONSENT TO STORE AND SHARE GENOMIC DATA FOR ANALYSIS

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EXECUTIVE SUMMARY

TABLE OF CONTENTS

BACKGROUND

Recent advances in medical research have shown that understanding the genetic profile of diseased cells is significant in improving the treatment and prevention of serious medical conditions. Cancer is a genetic condition driven by heritable (germline) and tumour-specific (somatic) mutations. The ability to distinguish these mutations, enabled by next generation sequencing (NGS), has revolutionised cancer care. In particular, molecular profiling of cancerous tumours has the potential to assist clinicians in providing efficient and effective treatment, known as "targeted therapy". Comparisons between the tumour (somatic-only mutations) and the host tissue can identify targets for therapy, which can improve disease prognosis. This concept was first demonstrated by Druker et al. (2006) using the drug imatinib to target a specific gene variant in chronic myeloid leukaemia. NGS technology is now routinely utilised in oncology to screen for genes known to be associated with improving treatment response, bridging a new era of chemotherapy and targeted treatment.

In parallel, NGS platforms are also integral to translational cancer research in identifying and validating promising new biomarkers for the development of cancer treatment. Worldwide collaborative efforts such as The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC), have catalogued the genomic landscape of thousands of tumours. In such settings, germline DNA has been routinely collected for comparative analysis with tumour DNA from the same patient, to unambiguously distinguish true somatic mutations from rare germline polymorphisms. For such research focuses, the main purpose is to identify tumour alterations with the analysis of germline variants being deemed secondary. However, some of these mutations occur in genes associated with inherited syndromes. When a clinically relevant germline variant is identified, the process of managing these germline findings has been extensively debated, in particular around if and when to communicate these findings to patients.

Clinical practice is currently shifting towards a preference of routinely sequencing tumour tissue alone to characterise its molecular profile for reasons including cost reduction and simplifying the logistics of sample collection (Catenacci et al. 2015; Jones et al. 2015). Sequencing a patient's tumour tissue alone is likely to challenge accurate delineation of somatic versus germline mutations due to the heterogeneous nature of mutations observed in tumours. For tumour suppressor genes, cancer causation is best described by Knudson's "two hit" hypothesis whereby a cell incurs mutations in both alleles, the first either germline or somatic, followed by a subsequent somatic event (Knudson et al. 1971; Vogelstein et al. 2013). Yet, for oncogenes, only a heterozygous mutation may be sufficient to regulate cell growth, and the initial event may be either somatic or germline. Therefore, it is possible that tumour genomic testing may

identify germline variants as they have been shown to occur in 3-10% of unselected tumour/ normal pair studies (Jones et al. 2015; Schrader et al. 2015).

Currently, there is no clear guidance on whether or how findings that only imply germline variations from somatic tumour profiling should be returned to patients. International governance bodies, such as the World Health Organisation (WHO) and the Organisation for Economic Co-Operation Development (OECD), as well as national regulatory authorities around the world have issued guidelines on genetic databases; although few have developed explicit guidance on the return of incidental findings (Zawati and Knoppers 2012). These guidance documents also only address the return of germline findings that may have health implications for individual participants as well as their genetic relations. None address the situation where tumour profiles results in a potential, but unconfirmed germline finding.

In addition to the uncertainty around managing incidental findings, the need for sharing biomolecular data internationally is increasingly being recognised as critical to understanding the role of genetics in oncogenesis and delivering more effective target therapies for cancer (Knoppers et al. 2011). However, researchers require common guidelines to ensure accountability and ethical oversight for the protection of patient data that is shared between institutions and across international borders (Knoppers et al. 2011; Caulfield et al. 2008). Recommendations from the US Presidential Commission for the Study of Bioethical Issues focus on establishing "strong baseline protections while promoting data access and sharing", "data security and access to databases", "a well-developed, understandable informed consent process", all the while "facilitating progress in whole genome sequencing" for the public benefit (Presidental Commission for the Study of Bioethical Issues 2012).

In 2014, the Global Alliance for Genomics and Health (GA4GH) was formed to create common frameworks to promote the ethical, responsible, voluntary, and secure sharing of genomic and clinical data. The Framework for Responsible Sharing of Genomic and Health-Related Data (Global Alliance for Genomics and Health 2014) established a set of foundational principles for sharing genomic and health-related data, namely:

- Respect Individuals, Families and Communities
- Advance Research and Scientific Knowledge,
- Promote Health, Wellbeing and the Fair Distribution of Benefits
- Foster Trust, Integrity and Reciprocity

These principles are elaborated in policies to guide specific issues and establish best practices on ethical governance, privacy protection, data security and informed consent. According to this Framework, best practices for the sharing of genomic and health-related data should “promote and protect respect for the commitment to informed consent” as the foundational principle that underlies the ethical conduct of all research involving human subjects (Global

Alliance for Genomics and Health 2015a). However, while intended to facilitate compliance with international norms, these policies should also be interpreted in a manner that recognises local cultural practices and the different contexts for storing and sharing data.

THE POLARIS DISCOVERY PROFILE

POLARIS (Personalised OMIC Lattice for Advanced Research and Improving Stratification) is part of A*Star's Genome Institute of Singapore (GIS) that aims to introduce and embed personalised medicine in Singapore. In collaboration with clinicians and scientists at GIS and Singapore Health Services (Singhealth), POLARIS has developed a College of American Pathology (CAP) certified panel of 93 genes identified from a comprehensive review of genes biologically and clinically relevant to gastrointestional (GIST) cancers (shown in Appendix One). Of these, five genes (*KRAS*, *BRAF*, *NRAS*, *KIT*, *PDGFRA*) are regarded as standard-of-care for predicting the efficacy of existing molecular therapies in GIST cancers and have been validated for clinical use (Wang et al. in press). This test is available for the clinical management of GIST cancer patients. At the request of clinicians, this test will assay tissue stored from tumour biopsy, and deliver a report on the variants found in the five clinically actionable genes described above. This clinical report is known as the POLARIS Tumour Profile and will be returned to the clinician to guide decisions on the best course of chemotherapeutics for the patient.

The POLARIS Discovery Profile will propose to assay the same tumour tissue for additional genes that have previously been reported in the literature as having potential, but unestablished, value in the diagnosis and treatment of malignancies. Currently, there are 88 proposed genes included in the Discovery Profile, which may increase in future as more research is published on cancer genetics and pharmacogenomics. Of these genes, 19 are of germline susceptibility and are deemed clinically actionable by the American College of Medical Genetics and Genomics (ACMG) (Green et al. 2013). Eight of these genes are known to predispose to colon cancer while the remaining eleven are associated with inherited syndromes not commonly associated with colon cancer development (shown in Appendix Two).

With the informed consent of participants, the Discovery Profile will be stored at POLARIS for future research purposes and shared with other researchers, both within and outside of Singapore. However, ethical and legal frameworks for obtaining informed consent to store and share genomic data in the context of Singapore are under-developed and currently rely on overseas models that may not be applicable to local laws, norms and practices. For instance, the collection, use, and storage of personal data by organizations are regulated in Singapore under the Personal Data Protection Act (PDPA) of 2012. The PDPA requires written or verbal consent to collect and store any data that can identify individuals, which may include combinations of sex, postal code, ethnicity and date of birth. As POLARIS will store the

participant's date of birth and their National Registration Identity Card (NRIC) number, the consent process will need to comply with this Act. Attention also needs to be given to what defines identifiable data as this varies amongst countries according to their population distribution. Given its small and relatively homogenous population, Singapore is considered to have a high re-identification risk range based on population and ethnic diversities. Specifically, personal data such as sex + ethnicity + date of birth + postal code or sex + ethnicity + date of birth + cancer diagnosis can uniquely indentify an individual from the Singapore population (pers comm). These identifiers have been considered for the storage of patient and tumour profiling information in the POLARIS databank as well as the sharing of this data externally.

In 2015, the Singapore government also enacted the Human Biomedical Research Act (HBRA), which will come into effect in 2016. The HBRA will regulate all human subject research (except clinical trials), including research with identifiable data. The Act includes provisions for written informed consent and the return of incidental findings (Government of Singapore 2015). Findings that have germline implications may also impact health insurance access for participants and their family members. Questions of whether and how the results of the Discovery Panel should be returned to patients, and how any incidental findings should be managed with respect to the national healthcare system are unclear and should be considered in developing of a framework for obtaining informed consent.

This study aims to develop an evidence-based framework for obtaining informed consent to store and share the POLARIS Discovery Profile data and make recommendations on the return of individual results and incidental findings. The study will draw on the prior literature in bioethics, social science, and best practices in biobanking and genomics, to develop a framework that reflects internationally accepted norms and standards for obtaining informed consent for the storage and sharing of genomic data from tumour tissues. The study will also employ qualitative research methods to engage clinicians and potential participants, and generate a contextualized framework that is culturally-appropriate and sensitive to local norms, systems and preferences. Findings from this research will inform recommendations on the process and documentation needed to obtain informed consent for the POLARIS Discovery Profile and share data with researchers in Singapore and abroad, and the possibility of returning individual results and incidental findings to participants.

RESEARCH QUESTION

The aims of the study will be met by addressing this research question:

How should informed consent be obtained to store and share genomic data from cancer patients in Singapore for research purposes, both domestically and internationally?

The key objectives of the research are to:

1. Explore the understandings, attitudes and preferences that cancer patients in Singapore have towards consenting to the storage, and sharing of genomic data for research purposes, both domestically and internationally, and receiving individual research results and incidental findings.
2. Describe the attitudes and preferences that clinicians have towards the process of obtaining informed consent to store and share genomic data from cancer patients in Singapore for research purposes, both domestically and internationally, and returning individual research results and incidental findings to participants.
3. Develop a framework for obtaining informed consent to store and share genomic data from cancer patients in Singapore for research purposes, both domestically and internationally and make recommendations for returning individual research results and incidental findings.

SCOPE OF THE REPORT

While this report draws on the bioethical and social science literature that has previously been published on international best practices for obtaining informed consent and returning research findings from genome and biobank research, this study is primarily focused on developing an evidence-based framework for the implementation of the POLARIS Discovery Profile in Singapore. The study will examine the understandings, attitudes and preferences that these patient cohorts have towards the Discover Profile, and giving their informed consent to share and store the data, both within Singapore and abroad, and receiving the results of the tumour profile analysis. Participants will initially be recruited at the National Cancer Centre Singapore (NCCS) from patient cohorts who have been diagnosed with colorectal or GIST cancer and have elected to assay their tumour type with the POLARIS Tumour Profile. However, breast cancer patients will also be included as this test may become suitable to a wider range of cancer patients in future.

The study will also examine the preferences and attitudes of clinicians staffed at the NCCS. As these individuals are likely to be the clinical oncologists and senior management at the NCCS, the study will target those individuals. These individuals will be consulted to identify other

relevant clinicians to include in the study. Discussions with both the patient cohorts and clinicians will inform the recommendations made in the report and development of a framework that is culturally appropriate and relevant to context of Singapore, and ethically defensible within internationally accepted norms and best practices in obtaining informed consent for genome databank research.

LITERATURE REVIEW

An ethical framework for obtaining informed consent from cancer patients in Singapore to store and share genomic data for research purposes, and potentially return results and incidental findings to participants, requires guiding principles to articulate the norms and values that should underpin these practices. In this review, the guiding principles for this framework are identified from the literature in bioethics on the ethical conduct of human subject research involving genetics and genomic technologies. Development of an ethical framework for the Discovery Profile will also require an understanding of local norms and practices within the situated healthcare settings of Singapore, and the challenges of obtaining informed consent from participants. Searching for literature on the specific context of Singapore, it appears that very little research has been published. Therefore, this review will consider empirical research that has been published elsewhere on genomic-related studies and initiatives to identify issues that may impact the informed consent process and recommendations for the return of research results and incidental findings.

GUIDING ETHICAL PRINCIPLES FOR GENOMIC RESEARCH

Much work in bioethics has been committed to the articulation and evaluation of norms and principles that guide the ethical conduct of research with human subjects. These principles have largely extended from the field of medical ethics, which asserts moral values and judgments in clinical decision-making, to human subject and biomedical research through the commission of the Belmont Report. This Report was commissioned by the United States (US) Health and Human Services (HSS) in 1979. One of the fundamental ethical principles articulated in this report is *Respect for Persons,* which requires individuals to be treated as autonomous agents and given the freedom to make choices and to take actions based on personal values and beliefs (Beauchamp and Childress 2001; p. 63). This principle is expressed in the need to obtain informed consent from participants to be subjects in any biomedical and medical research, which includes genomics and genetic technologies. Beauchamp and Childress (2001; p. 77-80) describe five basic elements needed for an informed consent:

1) Competence (ability to understand and decide)
2) Disclosure (of material information)

3) Understanding (of information disclosed)
4) Voluntariness (in deciding without coercion)
5) Consent (making the choice)

While these requirements are generally accepted, and have been formalized in legislative instruments that regulate human subject research in many industrialised countries, including Singapore, their application to specific contexts is often challenged by a range of social, cultural and situational factors. These factors can undermine the autonomy of participants to give a valid informed consent, and thus the ethical justifications for research (O'Neill 2002). For example, the institutional and cultural practices of medicine can influence the quality of consent that is obtained from patient cohorts recruited in clinical settings. In Asian contexts, this influence may be exacerbated by the heightened role of family in medical decision-making amongst Chinese (Cong 2004) and paternalistic patient-doctor relationships that are prevalent in India (Yousuf et al. 2007). In many Asian cultures, family members are often informed about diagnostic results and clinical findings before the patient (Yousuf et al. 2007). Clinicians in Singapore are frequently asked to withhold a cancer diagnosis from patients (Tan et al. 2011). If patients are unaware of their cancer diagnosis, they cannot possibly give an informed consent to take part in tumour profiling research.

Many other factors can influence the validity of informed consent in research, especially in genetics-related studies where familial considerations and cultural beliefs about illness and inherited diseases are often extremely important (Rotimi and Marshall 2010). Consideration of these factors were emphasised in the recommendations made in the 2005 report of the Singapore Bioethics Advisory Committee (BAC) on the *Ethical, Legal and Social Issues in Genetic Testing and Genetics Research.* In this report, the BAC (2005; p. 8) stresses the importance of free and informed consent, but also states that genetics research should be "conducted in a manner that is respectful of the welfare, safety, religious and cultural perspectives and traditions of individuals":

> "In a multi-cultural and multi-religious society, healthcare professionals and researchers must be sensitive to the religious and cultural perspectives and traditions of individuals. For instance, certain cultures may be particularly sensitive to the presence of a hereditary disorder in a member of the family. Any communication of this nature should be carefully managed. Similarly, in selecting a population group to be screened, it is important to avoid stigmatisation of the entire group."

While the POLARIS Discovery Profile will only analyse the mutations of tumour tissue without any germline comparison, the difference between somatic and germline mutations may not be well understood by prospective participants and their family members who will likely to be

accompanying them in the clinical healthcare settings of Singapore. Inviting members of the family to observe the consent-taking process may be a culturally-appropriate way to respect the persons who agree to participate in this research; however, researchers should also be mindful of any culturally-sensitive beliefs about the participant's cancer diagnosis and that family members should not unduly influence the patient's decision to participate. Respect for persons in these contexts may mean that "individuals remain free to act in ways that demonstrate the embeddedness of collective interdependence in their families, communities, and society" whilst still ensuring that participants are free of coercion and conflicts of interest when consenting to research (Gostin 1995 p. 845).

Indeed, the inherent limitations of obtaining an informed consent that meets the criteria set out in Beauchamp and Childress (2001) challenges the idea that respect for individual autonomy should be the prevailing principle that guides genomic research. Rather than relying on processes that may, at best, provide a *relevantly* (rather than *fully*) informed consent, Onora O'Neill (2002) argues for the adoption of 'principled autonomy' and its commitment to relations of trust as the ethical basis for genetic technologies and research. This approach invokes principles that require commitments to reject coercion and deception in genomics research because these practices fundamentally undermine relations of trust, which forms the basis of all ethically justifiable research. The rejection of coercion and deception may be expressed in refraining from deliberate misinformation, false promising, misrepresentation and fraud, or:

> More positively, it will be expressed through truthful communication, through care nor to mislead, through avoidance of exaggeration, through simplicity and explicitness, through honesty in dealing with others, in a word, trustworthiness (O'Neill 2002; p. 98)

Taken together, these commitments can provide the basis of informed consent requirements as providing research participants with a measure of protection against coercion and deception, rather than merely offering individuals the opportunity to sign a consent form in expression of their autonomy. Within this approach, the process of consent-taking remains important but it forms only one aspect of trustworthy practices. To promote and protect trust with research participants, institutions must also enact other ethical principles to ensure that participants are protected from unnecessary harms (non-maleficence) and that the research has value as public goods. Other emergent ethical principles that are being emphasised in the context of genomic research are reciprocity, mutuality, solidarity, citizenry and universality (Knoppers and Chadwick 2005). How principles such as these can apply to an ethical framework for obtaining informed consent the POLARIS Discovery Profile will be considered in this present study, along with the situational and contextual factors can that limit participant autonomy in the healthcare settings of precision oncology in Singapore.

OBTAINING INFORMED CONSENT FOR STORING AND SHARING GENOMIC DATA

To understand the types of issues that can impact on the quality of consent and trust relations with research participants, prior empirical research into current practices of obtaining informed consent to store and share genomic data is reviewed. This research was identified from searches of online databases, including PubMed, Google Scholar, and Medline using the keyword terms of "informed consent" and "genetic testing, whole genome sequencing, ethics, genetic testing or molecular profiling". While no prior research in Singapore was identified, and only a few studies related specifically to tumour profiling for precision oncology, considerable research has been done in related areas of biobanking, genetic testing and genome sequencing. These studies will be discussed with reference to the challenges of obtaining informed consent and the proposed solutions to these problems.

Understanding and Information in the Consent Process

Two major challenges frequently identified in the literature is how informed participants are when consenting to take part in genome research and the nature of information that should be provided to them throughout the consent-taking process. Both issues relate to the model of consent that large-scale biobanks and genomic databases have generally adopted for the longitudinal storage and sharing of biodata for research. These models are typically described as broad or blanket consent, although the literature often applies these terms inconsistently and interchangeably with other terms, such as general and open consent (Hansson 2009). For the purposes of this study, the relevant conceptual models of consent are defined according to the increasing levels of control they impart to participants:

- Implied: Consent is not explicitly sought from participants.
- Blanket: Consent is sought once from participants for any future research without the need obtain any further consent.
- Broad: Consent is sought from participants for use in any future research without the need obtain further consent from the participant, who then delegates their decision making authority to an IRB (or another institution) for specific research projects.
- Categorical: Consent sought from the participant for particular categories of research; may include options that allow recontact with participants to consent for research outside of the nominated areas.
- Specific: Consent sought from the participant for specific research projects only; may include options that allow recontact with participants to consent for research outside of the nominated areas.

Many longitudinal biobanks have adopted broad consent regiments due to the impracticalities of recontacting large number of participants over the long-term for specific research projects (Master et al 2012) and statutory requirements for independent review from an IRB. This

model departs from traditional norms of consent where participants must be fully informed of the nature and risks of a specific research project. While numerous scholars have argued for the ethical justification of broad consent regiments (Hansson et al. 2006), others argue that they cannot constitute an 'informed' consent (Caulfield 2009) and they breach conceptions of autonomy as an opportunity for protection and deliberation (Hoffman 2009). However, many scholars have at least acknowledged that traditional norms of consent are unlikely to be satisfied or sufficient in the context of genome research and must be supplemented with governance structures that can ensure transparency and accountability over the consent process (Caulfield et al. 2008).

In their consensus statement on NGS research, Caulfield et al. (2008) recommend:

> Prior to participation in a whole-genome project, participants should be asked to provide consent for future use that includes as much detail as possible, including information about the sampling and sequencing process, associated commercialization activities, possible risks, and the nature of likely future research initiatives. The consent process should also include information about data security and the governance structure and, in particular, the mechanism for considering future research protocols. When deemed appropriate by the governance scheme, reconsent for specific research projects may be required (e.g., when the proposal deviates significantly from what was stated in the initial consent).

The prior research suggests that there is a high degree of consistency in the types of information that are given to participants during the consent process (Allen and Foulkes 2011). A systematic review of the literature on obtaining informed consent to store genome sequencing data generated in clinical settings for research found that, at the very least, participants should be informed about: the scope and purpose of the databank, the risks and benefits of participating, voluntariness, privacy and confidentiality protections, the duration of storage, the collection of basic personal information and access to medical records, possible future research uses, withdrawal options, the return of incidental findings, and the right not to know (Ayuso et al. 2013).

Yet several studies have shown that the understandings participants have about the nature of genetics and the research they consent to can vary widely. Studies in the US suggest that while many people have a general understanding of familial genetics, the underlying concepts can be harder to grasp (Lea et al. 2011). Participants are also often confused about the differences between somatic and germline testing (Kaphingst et al. 2012; McGowan et al. 2014) and the respective risks and benefits of each (Gray et al. 2012). Kaphingst et al. (2012) argue that these understandings are related to education levels and that knowledge of genome sequencing can be significantly improved when consent documents are delivered and explained by a trained genetic counsellor. However, such an approach would rely on the availability of resources to support suitably qualified personnel to counsel potential participants, which may not be

appropriate for tumour research where the majority of the mutations would derive from somatic origin. It is also unclear whether the same result could be achieved with a research co-ordinator or nurse knowledgeable in cancer genomics who has the time to spend with prospective participants in explaining the differences between somatic and germline mutations, and answer questions sufficiently prior to taking consent.

Assumptions about the relationship between a participant's education or knowledge of genetics or science/health/medicine, and their willingness to consent to genomic research reflect the long-discredited 'deficit model' of public understandings of science and technology. This model assumes that knowledge of science leads to support for scientific research and its technological products, and that a lack of support reflects a deficit in knowledge (or ignorance) that can be remedied by simply providing more 'correct' information (Felt 2000; Wynne 1992; Michael 1996). However, the empirical evidence suggests that these assumptions are not well-supported. For instance, Sturgis, Brunton-Smith, and Fife-Schaw (2010) found that providing value-neutral information to random samples of the British adult population had no effect on their attitudes toward genetic science but was significantly associated with less educated participants dropping out of the study. Their results suggest that simply providing information to potential participants in genome research may bias genome studies towards a more highly educated cohort.

Indeed, the increasing complexity of consent forms and information sheets in genome research has been criticised and scholars have argued for greater simplification in order to improve participant comprehension and understanding of the research they consent to (Beskow et al. 2010). Beskow et al. (2010) suggest that electronic tools can help deliver simplified consent forms that allowing participants to control the amount of information they access with links to more comprehensive supplementary information about the research. To avoid over-burdening participants with information, particularly in clinical settings, Bradbury et al. (2014) suggests that information be tiered according to its relative importance: tier 1 being essential information that should be presented to all participants, with tier 2 being more specific information that can be accessed optionally to support the variable informational needs of diverse populations and ease decision-making.

The Context of the Consent Process

Notwithstanding the importance of providing clear and sufficient information, the literature also points to other contextual and situational factors that will likely impact the consent process in Singapore. According to the BAC (2005) Report on genetics research:

> "Consent is only effective if the person giving the consent is aware of the circumstances, conditions and consequences for which it was given. How an individual may be appropriately

informed prior to giving consent to testing depends on the situation in which consent is sought and the comprehensibility of the language used in the interactive process."

Arguably the most important situational factor for the POLARIS Discovery Profile will be the clinical settings where participants will be recruited and their consent taken. Research has shown that seeking consent during a stressful period following a cancer diagnosis or when surgery is being proposed can severely undermine the quality of informed consent (Scollon et al. 2014). Furthermore, if medical oncologists are handling the consent process, patients may confuse the research with their clinical care and not fully comprehend what they are consenting to (Miller and Rosenstein 2003). This can invite therapeutic misconception, which occurs when participants believe that the research they have consented to is aimed at benefiting their individual treatment, rather than producing generalizable research findings (Appelbaum et al. 1987; Lidz and Appelbaum 2002). These misconceptions can often occur when the goals of the research are conflated with goals of clinical care.

Conflating clinical care with research could also cause misunderstandings amongst participants about the risks and benefits of taking part in the research, and they may consent with the mistaken belief that it will impact on the quality of care or treatment they will receive (Grady 2015). Such perceptions not only invite therapeutic misconception, but if participants believe they will not receive quality care unless they do consent, there may be grounds for coercion. This prospect would not only undermine respect for autonomy, it may also damage relations of trust with participants and patient cohorts, especially if these practices are perceived as deceptive. As argued previously, protecting and promoting trust in research will be essential for fostering widespread participation in these types of studies (Beskow and Dean 2008b).

Yet, disentangling the aims of research from the clinical settings where many participants are (often necessarily) recruited can be extremely difficult. For example, patient cohorts may be essential in meeting the aims of the research and recruiting them off-site may be highly impractical and inconvenient for participants. Moreover, patient cohorts are inherently vulnerable and are often willing to take part in research in desperate hope of better treatment even when no such benefits can be derived from participating. However, excluding patients from research, or only recruiting patient cohorts from outside of the clinic settings they are identified from is neither a realistic or desirable solution. In many cases, patients may only benefit if research is done on the same patient groups recruited under these circumstances. Indeed, evidence suggests that solidarity with imagined future patients strongly contributes to patient-subject decisions to take part in research (Felt et al. 2009). Solidarity in this context can be described as "manifestations of a collective commitment to carry costs to assist others (who are all linked by means of a shared situation or cause" and the concept is frequently used to justify the use of broad consent for large, longitudinal biobanks" (Nuffield Council on Bioethics).

Prior research on biobanks suggests that participants may generally prefer a blanket or broad consent regiment (Pentz et al. 2006; Helft et al. 2007). However, these preferences are context dependant and have been found to correlate strongly with trust in the institutions that host the facility (Nilstun and Hermeren 2006; Tupasela et al. 2010; Kettis-Lindblad et al. 2006; Levitt and Weldon 2005; Pulley et al. 2008; Beskow and Dean 2008a; Goldenberg et al. 2009; Leiman et al. 2008; Lipworth et al. 2009). The prior research typically reports low levels of recall and interest in the information that is given to participants, who readily appear to sign consent forms based on trust (Skolbekken et al. 2005; Tutton 2007; Hoeyer et al. 2005; Haimes and Whong-Barr 2004a; Hoeyer 2004; Barr 2006; Ducournau 2007). This is particularly the case where participants are recruited in clinical contexts (Hoeyer 2003; Haimes and Whong-Barr 2004b; Hoeyer and Lynoe 2006). Participants may also place greater trust in institutions and research that is perceived to be for 'public good' (Allen and McNamara 2009), and might not agree to broad consent if the research was intended for commercial exploitation (Vermeulen et al. 2009b) or for purposes that participants would morally object to (Neidich et al. 2008; Secko et al. 2009; Kaufman et al. 2009; Murphy et al. 2009; Goldman et al. 2008).

These observations have led many scholars to argue that an over-emphasis on information is inappropriate for genomic research, and that focus should shift away from the obligation of individuals to make informed choices and towards the responsibilities of institutions to nurture and maintain trust relations between research institutions and participants. Rather than treating consent as a means of empowering individuals, it may be more appropriate to enact the process as a part of a moral negotiation that takes place in a context whereby an individual's sense of responsibility can be mobilized to gain access to research participants; particularly in clinical settings (Hoeyer 2003). Because even though some participants may see the consent process as an unnecessary formality serving to protect the interests of research institutions rather than the welfare of participants (Ducournau 2007; Asai et al. 2002), many others will see it as a sign of respect (Hamilton et al. 2007) and consider themselves as autonomous agents choosing to take part in a moral act (Allen and McNamara 2009).

This argument does not suggest that consent may be implied as many individuals will at least want the opportunity to say no or to withdraw consent later (Vermeulen et al. 2009b; Vermeulen et al. 2009a). However, the argument does lend support to processes that demand more from institutions than simply providing information to participants and getting their signature on the written consent form. This requires an honest, transparent and non-coercive process using information that is comprehendible. In this context, consent becomes symbolic of the trust that participants invest in researchers and research institutions (Allen and McNamara 2009). Therefore, if a broad consent regiment is adopted for the POLARIS Discovery Profile, practices of maintaining trust with participants should be implemented to ensure that the data is stored and shared within the moral parameters the consent was given.

Withdrawal from Genomics Research

A final issue to be considered in the consent process is the provision of withdrawal options. In many jurisdictions, including Singapore, the ability of participants to withdraw their consent from biomedical research evolved from the Nuremburg Code (1949) an ethical standard into a legally enforceable right. In Singapore, the right to withdraw is formalised in Section 14 of the HBRA (Government of Singapore 2015), which states that:

> "A research subject or any person who is authorised to give consent on the subject's behalf under this Part may, at any time, withdraw the consent to the subject's participation in the human biomedical research"

For genome research, however, it is recognised that the integration of data across multiple sites and the rapid dissemination of results can make it highly impractical for this right to endure (Caulfield et al. 2008). These difficulties are exacerbated when the data shared are de-identified or anonymised and links to participant's contact information is severed. While efforts can be made to enable the right to withdraw for as long as practical, participants must be made aware of these limitations when consenting. The consent forms for many databanks state that while participants may withdraw at any time, and their data will not be used for any future research, any data already shared with other researchers could not be destroyed (Allen and Foulkes 2011). This approach is consistent with the GA4GH Consent Policy (Global Alliance for Genomics and Health 2015), which states that while consent materials must specify how participants in genome research can withdraw but that it may be impossible to retrieve and/or destroy data that has already been shared.

As genomic data is a valuable resource, even when not linked to personal information and medical records, some facilities offer multiple withdrawal options. Multi-tiered options can allow a participant to sever the links to personal information, while still allowing the facility to use and share the data for research purposes. McGuire and Beskow (2010) describe four different levels of withdrawal: no more contact, no more access, unlink and no further use. All these methods have different levels of implications for genomic data, which researchers should carefully explain to participants who seek to withdraw from the databank.

To help manage multi-tiered withdrawal options, some large scale longitudinal databanks have employed electronic informatics in a so-called 'dynamic' consent process, which is increasingly being viewed as best practice especially for complex protocols that involve the sharing of data and potentially recontacting participants with research results or incidental findings (Kaye et al. 2015). Kaye et al. (2015) argue that dynamic consent processes better fit the purpose than the traditional static consent model where participants typically give a one-off (usually) broad consent without truly understanding the aims, hypotheses or nature of the future studies that

might access their samples and/or data, or the information that might one-day be returned. However, while this dynamic model is intuitively appealing in promoting the autonomy of research participants, it has also been criticised for, among other things, the risk of inviting therapeutic misconception and weaker ethical review of specific research projects (Steinsbekk et al. 2013). The costs of implementing and maintaining such a system would be a limiting factor in how well participants remain engaged and thus, truly informed throughout the process. The effectiveness of these systems may also be limited within the context of precision oncology in Singapore, where the demographic of participants will generally be an older population with variable levels of education, language capabilities and access to the technologies needed to facilitate a dynamic consent and withdrawal procedure.

RETURNING INDIVIDUAL RESULTS AND INCIDENTAL FINDINGS

The return of individual research results and incidental findings has been debated extensively in the literature on biobanks and genomic research; currently there no consensus on how these should be managed (Zawati and Knoppers 2012). Both, individual research results and incidental findings, can reveal potentially important information about the health of individuals. In a genetics context, they can also have social and medical implications for an individual, their family and/or community (Townsend et al. 2012). However, they differ in important ways. Research results are generated in course of meeting the stated research aims (Wolf et al. 2012), and can generally be interpreted by researchers; whereas incidental findings are exogenous to the aims of the study and interpretation and usually requires clinical expertise and consideration of the individual's medical and familial history (Wolf et al. 2012). The possibility of generating either complicates the informed consent process because researchers must anticipate the types of findings that might be disclosed and determine which of those, if any, should be returned, and how.

In genomics research where data has been collected for longitudinal studies, it generally has not been standard practice to return individual research results directly to participants. Although some biobanks that recruit in clinical settings have returned them indirectly via the treating physician or directly to patients advising to seek professional advice from a healthcare provider (Wallace and Kent 2011). Two arguments against returning results directly to participants are prevalent in the literature: 1) research data are not clinically valid and thus have limited clinical utility; and 2) promising individual findings may promote therapeutic misconception and incentivise participation inappropriately (Zawati and Knoppers 2012). In Singapore, the BAC has explicitly discouraged the practice, stating that:

> "…donors should not expect any personal or direct benefit from the donation of tissue, including information of any medical condition or predisposition or likelihood of such discovered in the course of research on the sample. Likewise, researchers and tissue bankers should not be under

> an obligation to disclose such information to the donors, unless they have agreed to do so in advance of the donation" BAC (2005)

Similar arguments have been made against returning incidental findings, although they have increasingly been challenged due to the seriousness of their potential health implications. Examples of incidental findings include non-paternity or susceptibility to diseases that may or may not be clinically relevant or actionable within currently accepted standards of care. Returning such findings to participants raises questions of privacy and confidentiality, as (re)identifiable links to individual data must be maintained, as well as issues of false positives, discrimination, and the right of individual, family or community not to know grave information, especially if the findings are not clinically actionable (Androno, 2004). However, some scholars have argued that there is a duty to rescue or to intervene in cases of urgency and when the intervention is relatively easy to provide with minimal risks (Belsky and Richardson 2004; Richardson 2008). This situation would not arise frequently, and this duty fails to recognise participant preferences when they have not consented to receive this information.

While patients may have preferences to receive research results and/or incidental findings (Meulenkamp et al. 2010), health care providers may not be sufficiently trained for the disclosure (Devon et al. 2015; McGowan et al. 2014), in particularly if they relate to complex medical genetics, which raises concerns about additional infrastructure requirements and costs (Townsend et al. 2012; Ross and Reiff 2013; Kleiderman et al. 2014). In addition, this creates an increase of workload outside their clinical obligations. There are also concerns about burdening vulnerable populations with information that may cause unnecessary worries. To alleviate these concerns, some researchers have suggested restricting reportable variants to those of known clinically actionable items or letting participants select a disclosure policy (Tabor et al. 2011; Bredenoord, et al. 2011; Hall et al. 2013; Kleiderman et al. 2014). Bredenood et al (2011) suggests offering a default package of results containing life-saving or immediately clinically actionable data. Most notably, ACMG has recommended a list of 56 genes deemed clinically actionable and advise that these should be reported to patients, even if mutations in these genes are discovered in research settings (Green et al. 2013). Whether researchers intend to return the results or not, it is advised that participants are made aware of this by it being clearly stated in the consent form, and if results are made available, that patients have the choice to receive them (Wallace and Kent 2011).

Whilst there have been several proposals around returning incidental findings generated from tumour and germline testing (Bombard et al. 2013), at this stage, the POLARIS Discovery Profile only intends to procure tumour samples without germline comparison. Discussions around variants found in hereditary genes from tumour profiling are only just emerging. To date, there have been at least three studies verifying cases of germline mutations detected from tumour

profiling (Catenacci et al. 2015; Meric-Bernstam et al., 2016; Varga et al. 2015,). The possibility of germline origin was considered in context of the gene mutation and its association with hereditary cancer as well as the availability of clinical information, such as tumour histology, age of diagnosis and family history. The possibility of an incidental finding was disclosed to research participants and germline testing was offered following genetic counselling. These studies was conceded that tumour NGS is an additional indicator of germline mutations. This view has also been supported in a recent commentary which has developed recommendations for laboratories regarding the detection, analysis and reporting of potential germline variants, as well as clinicians acknowledging that tumour profiling may detect hereditary variants and how this should be approached with patients (Raymond et al. 2016). Whatever policies are implemented for the POLARIS Discovery Profile, prospective participants should be informed of these possibilities prior to consenting and a plan to manage the disclosure is implemented.

There is much discussion in the literature on best practices for the informed consent process in genomic testing. The extensive review of the literature provides a foundation for the empirical work to develop a Singapore specific informed consent process for the POLARIS Discovery Profile. The literature provides guidance on the type of informed consent model, the return of results and management of incidental findings. Most of the literature is from the United States, Australia or Europe; nothing exists understanding the viewpoints and preferences of stakeholders in Singapore. This study will address important gaps in literature as the POLARIS Discovery Profile is implemented.

METHODS

RESEARCH DESIGN

The study was designed with the aims of exploring and describing the attitudes, understandings and preferences that clinicians and cancer patients have towards participation in tumour profiling research, storage and sharing of tumour genetic data, and the return of research results. To achieve these aims, the study design employed qualitative research methods. Qualitative studies document and explain the variation in a wide range of views, needs, values, practices and beliefs (Denzin and Lincoln 2005). They are not designed to estimate proportions in a wider population, quantify relationships between pre-determined variables, or provide a single representative or average view or opinion (Kuper et al. 2008). They are, however, particularly useful for policy development and for the design and delivery of health care; and are especially suited to exploring the understandings and attitudes towards highly complex concepts and subjects that cannot be fully captured with quantitative methodologies.

The study was conducted in two overlapping phases to: 1) describe the attitudes and preferences of clinicians working either at the National Cancer Centre Singapore; and 2) explore the attitudes, understandings and preferences of cancer patients. The descriptive phase contributed to the drafting of documentation (i.e. the participant information sheet, consent form and a brochure) that was presented to patients during the interviews. Evidence gathered in both phases informed the development of an ethical framework for obtaining informed consent to store and share biomolecular data from cancer patients in Singapore for research purposes, and recommendations for returning research results and future incidental findings. Analysis of the empirical evidence is presented in the results, and the framework and recommendations are set out in the discussion.

Sources of Evidence

The sources of evidence in both descriptive and explorative phases were semi-structured interviews with clinicians and patients. Qualitative interviewing is an established research method that has been applied extensively in the social studies of science (Jasanoff et al. 1995), health policy (Grbich 1998) and empirical bioethics (Holm and Jonas 2004; Ives and Draper 2009). Semi-structured interviewing is an interpretative method that can provide researchers with a deeper and more contextualised dataset than structured interviews, whilst allowing the research to focus on specified issues under investigation (Denzin and Lincoln 2005). This method also allows for qualitative comparisons across the dataset and is most suited to inquiries that are narrowly focused. The goal is to generate themes from clearly defined, homogeneous populations within an already known context (Miller and Crabtree 2004). The

suitability of semi-structured interviews as a source of evidence in this study is justified by homogeneity of the target population as clinicians involved in consent collection and cancer patients at the NCC.

Ethics Approval

Ethics approval was obtained from the Domain Specific Research Board (DSRB) of SingHealth on 9th July 2015 to conduct up to 10-15 semi-structured interviews with Singhealth staff and cancer patients: (2015/2522). The original protocol included between 3-5 focus groups with patients. However, due to unforeseen changes in personnel, the focus groups were abandoned in favour of semi-structured interviews with patients. Approval to amend the research protocol and shift to interviewing cancer patients was obtained on 30th September 2015. Materials submitted to the DSRB are shown in the Appendices, which include the formal email sent to clinicians inviting them to participate in the study (shown in Appendix Three), clinician information sheet and consent form (shown in Appendix Four), patient information sheet and consent form (shown in Appendix Five), interview protocols for both clinicians and cancer patients (shown in Appendices Six and Seven) and the draft informed consent document reviewed by patients (shown in Appendix Eight).

DATA COLLECTION

Qualitative interview focus groups are carried out with small groups of participants and are not intended to generate a 'representative' or 'average' view or opinion. Therefore, random sampling was not warranted for this study. Instead, purposive sampling techniques were selected as they allow for greater flexibility in targeting participants and capturing a broad range of perspectives in the sample (Merriam 1988). This process involved identifying clinicians and emailing them for an interview and approaching patients directly at the NCC.

Recruitment

In order to identify relevant clinicians, clinical members of the research team (Dr. Iain Tan, Dr. Daniel Tan and Dr. Joanne Ngeow) provided a list of 25 key oncologists at the NCC to be interviewed. Three emails were sent to these individuals over three weeks starting at the end of July 2015. From these emails, a total of six clinicians responded agreeing to be interviewed; resulting in a response rate of 24%. To increase the sample, an email invitation was sent to additional 59 Singhealth oncology staff in early August. Of these 15 responded and 5 agreed to participate. This process resulted in a total of 11 participants being recruited from a pool of 74 contacts with a response rate of 14.8%, which is considered a low response rate for qualitative research. No further attempts were made to increase response rate as data became saturated

at 11 interviews. The interviews were conducted between July and September 2015 on the phone and face-to-face based on the preferences of participants.

For the patient group, the study aimed to recruit patients from the breast, colon and lung cancer clinics at the NCC. However, another somatic cancer test was being launched in the colon and lung cancer clinics at the same time as patient interviews were scheduled. To avoid confusion, only patients in the breast cancer clinic were interviewed. Eligible participants were recruited from the waiting room with the assistance of staff at the registration desk in the public clinic and nurses in the private clinic and offered a $50 supermarket voucher as fair compensation for their time. Of the 29 patients approached, only three declined to be interviewed; leaving a total of 26 participants. The much higher response rate of 89.6% in this group was likely due to the support of their treating physician, being present onsite, face-to-face recruitment and inducement. The patient interviews were conducted in October 2015.

Interview Protocol

An interview protocol for both groups was developed from the issues identified in the literature review (shown in Appendices Six and Seven). The clinician interviews were structured around three key issues to describe their attitudes and preferences towards:

1. How information on the cancer diagnosis and the role of genetics (if any) is delivered to the patient;
2. Delivery of the POLARIS Discover Profile details (both the clinical and research components); and
3. The type of informed consent document required with a focus on the language needed to explain storing, sharing and withdrawal of tumour profile data.

Even though the POLARIS Discovery Profile involves tumour-only analysis, clinicians were also asked about the incorporation of germline analysis in the event of current test expansion.

Clinician interviews contributed to the development of the participant information sheet and consent form, as well as a brochure that was designed as supplementary information to assist with patient understandings of tumour profiling and genomics research. These documents were given to the patient group in an interview protocol that was designed with greater flexibility to explore participant attitudes, understandings and preferences of key issues including: the purpose of the test; preferred linguistic labels and options of delivering the informed consent; the test procedures (sharing, storing and recontact for additional research); perceived benefits and risks; ideas of altruism and solidarity; attitudes towards withdrawal options; and role of family and medical professionals in decision making. The interview guide was piloted with one patient in the colon cancer clinic before full data collection proceeded.

DATA ANALYSIS

All interviews with patients and clinicians were digitally recorded, transcribed verbatim and analysed using qualitative content analysis to identify, categorize and interpret key themes in relation to the consent process for storing and sharing of biomolecular data. Qualitative content analysis is a common method used to examine data that is "the product of open-ended data collection techniques aimed at detail and depth, rather than measurement" (Forman and Damschroder 2007 p. 41). The analytical process involves deep immersion with the data and iterative refinement to generate categorical themes inductively that capture the key issues. The findings can then be explained within the theoretical frame laid out in the literature review.

Transcripts were read multiple times by the interviewer along with two study team members (Yasmin Bylstra and Tamra Maree Lysaght) to identify major themes and sub-themes. These themes and sub-themes were discussed together by the three study team members to corroborate categories and placement of relevant quotes. Quotations were highlighted to enhance the meaning of each theme and included in the results. There were minimal differences in interpretation of the qualitative data. Demographics (age, ethnicity, gender and type of cancer diagnosis) were also collected for each patient and analysed using basic descriptive statistics (averages, median and frequencies).

RESULTS

From August to October 2015, 11 stakeholders (7 oncologists, 2 cancer genetic specialists and 3 palliative care doctors) were interviewed at the National Cancer Centre (NCC).

Patients in both the private and public breast cancer clinic were recruited. In total, 26 patients were interviewed (shown in Appendix Nine). All but one was from the breast cancer clinic and female; the first patient interviewed was from the public colon cancer clinic and male. The average age of those interviewed was 52, with a median age of 54 years. The majority were Chinese, with Indian being the next largest group. The remaining were Malay (3), Bangladeshi (2), Malay/Chinese (1), Pakistani (1), Filipino (1), Vietnamese (1). Eleven patient interviews were transcribed with an average age of 54, median of 55 years (range between 39 and 69 years of age). Eight were Chinese and 3 Indian in origin. One was male and the remaining was female. The decision on which interviews to transcribe was based on the richness of the conversation.

INFORMED CONSENT AS A PROCESS

The process of obtaining informed consent from patients to take part in the Discovery Profile was discussed with patients and clinicians. These discussions centred on the length and complexity of the form, participation in research and sharing of biomolecular data, the management of research results and incidental findings, the type of preferred consent and withdrawal options. It was generally found that both patients and clinicians preferred that information be provided within a broad or blanket consent regimen with an option to withdraw from the research. However, the views of patients and clinicians on the possibility of returning research results and incidental findings to participants were more diverse with some disagreement between the two groups on how these should be managed.

Broad Consent as the Preferred Model

The various models of consent (shown in Appendix Ten) were not discussed with patients as many were found to have a limited understanding of the term “informed consent”; this finding is described in further detail below as a barrier. However, the clinicians were generally more familiar with the various types of consent regiments and were asked about their preferences as actors who would potentially be involved in the process of obtaining consent from patients for the Discovery Profile. All but one clinician felt that a blanket or broad consent would be most appropriate for this purpose. One clinician preferred a categorical consent out of concerns for sharing of genetic data outside cancer related research. However, most of the clinicians felt that documentation with multiple consent tiers would be confusing to patients and

cumbersome to manage; and all agreed that the information given to participants about the research should be comprehensive without being overly-complex.

> "It would be more easier for scientists or researchers to get the one that the patient already say "Okay, I agree you can use it freely for research" and cover all the parameters with the patient. It is easier for the researcher. For the patient, they will feel "Why I have to consent for so many things?" (Clinician 2)

Once participants provide their informed consent, they should also have the ability to withdraw from the research at a later time. The parameters of enabling participants to withdraw from the Discovery Profile were discussed with clinicians to determine how best to address this issue in the informed consent process. Tumour profile data can be deleted from the POLARIS database preventing future sharing of data. However, there will be difficulties in withdrawing data that have been already been shared, particularly if these data are de-identified. Clinicians were comfortable with these parameters and limits to the extent a participant can withdraw from the research so long as they were made clear in the information given to patients prior to obtaining their consent:

> "Honestly, all the research that you do…it is treatment or therapeutic study, the patient can withdraw from the therapy anytime. But always under guidelines that the data collected, they cannot withdraw from that part. So I think it is how you write the consent form. Honestly, logistically how are you going to withdraw the data? That is going to take another layer of work? "(Clinician 1).

Clinicians also believed that patients would have similar views and that comparable protocols already exist in current oncology practice where data, once released, can no longer be recalled. From their experience, clinicians explained that it was uncommon for patients to request withdrawal from clinical trials or research they were participating in and, therefore, did not believe that this situation would arise very often with the POLARIS Discovery Profile. Patients also did not seem to be concerned about the possibility of being unable to withdraw their Discovery Profile from databases completely and did not indicate any preferences to do so.

Return of the Discovery Profile and Incidental Findings

While the clinicians interviewed generally preferred a broad or blanket consent, they also expressed preferences for the inclusion of provisions for participants to opt into the return of the Discovery Profile and incidental findings. Some clinicians felt that participants should be given the option to receive the Discovery Profile as a matter of standard practice in the same way that other commercially available tumour profiling services were thought to return this information directly to patients, such as Foundation One. Some suggested that the results should be returned to both the participant and their treating oncologist automatically without the opportunity to opt out. However, not all clinicians agreed with this approach because the

information contained in the Discovery Profile was research and, therefore, would not be clinically actionable:

> I think if this information is not going to clinically benefit the patient, then it is irrelevant to them and will confuse the whole issue. And worry people. I think it is an extra burden. You give them all this information. What does it mean? It doesn't mean anything. Then why are you giving it to me?" (Clinician 10).

Patients, on the other hand, were clearer in their preferences to receive the results of the Discovery Profile. Many patients interviewed indicated a strong preference to receive the Discovery Profile and for their oncologist to explain the implications of the results. While some patients stated that they did not mind who delivered the results, and would accept another suitably qualified person to explain them, many indicated that it was not appropriate for nurses to do so. These preferences were expressed with a lack of confidence in the ability of nursing staff to answer questions about the research results sufficiently:

> "May not necessarily be a doctor, but maybe someone higher than a nurse. Yeah….Because sometimes you may have questions that the nurse may not… be able to answer certain questions. Um…a person who gives confidence that means a person who has experience in such research and studies. Then we will feel more comfortable. Because if the nurse were to give us, and we ask the nurse certain questions if the nurse give us a puzzled look or cannot answer the question then we do not feel very comfortable." (Patient 2)

Patients were less certain about participants being recontacted with future research results. It was acknowledged that information regarding genetic mutations and tumour development to inform optimal treatment is rapidly evolving. As research progresses, an improved understanding of the genes included in the POLARIS Discovery Profile may result in some being redefined as clinically actionable. However, patients had mixed views about being re-contacted with clinically significant results in future. The Discover Profile will be stored in the POLARIS databases for 10 years, but some patients felt that this time frame would be too long and that results might not be relevant to their disease at the time of re-contact. Others indicated that they would not want to be re-contacted given their age and stage of cancer for which they were currently being treated. Yet, some patients thought that the results might benefit them in the event of a future relapse while others placed value on potentially gaining a deeper understanding of the pathology of their cancer:

> "Yes, definitely. The hope would be that something changes and that there is something new or better. Even if we don't know what to do about it, just more understanding. "Oh, this is what causes it" as opposed to just bad karma" (Patient 7).

The clinicians were less open to the proposal of recontacting patients with future research results and were concerned about the practicalities of tracking down patients who may have moved or passed away since the original consent was given. Clinicians also had conflicting

views about the return of incidental findings. As the Discovery Profile panel contains genes that are associated with hereditary conditions, there is the possibility that mutations in these genes derive from germline origin. The prospect of identifying incidental findings generated conflicting ideas amongst clinicians. One clinician felt that putative germline mutations should be kept aside and not disclosed until the appropriate regulations and infrastructure changes were in place to counsel patients or to protect them legally from any potential future discrimination. Some clinicians felt that patients should know, but needed to be referred to another health professional trained in discussing germline implications:

> "I don't think I can hide this from the patient. You have to tell the patient. Patient's interest for me to tell them to get tested. This has implications for you. I will send you to a trained cancer genetics oncologist or counsellor or whatever to sort this out. It should not be done in my clinic. It has to be someone trained." (Clinician 10).

By referring to the consent declaration regarding the return of results, patients were asked their views regarding incidental findings. Patients did inquire about what type of incidental findings may appear in the Discovery Profile and were informed that these could include a risk to hereditary conditions such as bowel cancer or cardiac conditions. Patients were clear that they wanted to know about these incidental findings, yet they wanted to receive these by a trusted professional, such as a doctor. Patients felt that receiving such information independent of any explanation could create unnecessary confusion or worry.

If research results are returned to patients, the inclusion and management of such incidental findings must also be considered. These and other issues are described further below as potential barriers to obtaining informed consent and undermining the ethical justifications for the research.

BARRIERS TO INFORMED CONSENT

Throughout the interviews with both patients and clinicians, a number of issues emerged as potential barriers to obtaining informed consent from participants for the Discovery Profile. These barriers included the limited understandings that the target population would have about cancer genetics, and the difference between somatic and germline mutations, as well as what giving informed consent for the research would entail; especially if the process and documentation delivered to participants is limited to the English language. Others barriers related to the limited time that clinicians would have to discuss information about the Discovery Profile with patients and obtain their written consent, as well as the perceived conflation of the research with the clinical profile test, and therapeutic misconceptions. These results are indicative of the complexities that can be expected in managing tumour genetic information for clinicians, its perceived interpretation by cancer patients and how these can impact the process of obtaining informed consent for the POLARIS Discovery Profile.

Limited Understandings of Genetics and Informed Consent

Although the interviews were conducted in English, most of the patients interviewed had limited English and needed younger family members to translate. These language barriers are likely to complicate the informed consent process as it is unclear whether the participant will fully comprehend what they are consenting to. The comprehension of participants will depend on how well family members understand and translate the information given to them about the POLARIS Discovery Profile, which could be expected to vary. In the multi-lingual context of Singapore, translating the informed consent document into the three official languages, in addition to English, would reduce help to reduce these barriers.

Even then, some participants may experience difficulties in understanding what the provision of informed consent for research entails. As mentioned above, it became evident throughout the interviews with patients that most did not understand what was intended by "informed consent" when asked what they thought this term meant. Many patients responded that they did not know what was meant by informed consent, even though they had just reviewed the informed consent documentation and, indeed, had signed the consent declaration to participate in the present study before commencing the interview. This experience suggests that a substantial amount of time would be required to explain the purpose of informed consent for research participation to patients, even prior to presenting information on the POLARIS Discovery Profile.

The issue of comprehension was even more pronounced in discussions with patients about cancer genetics and tumour profiling. None of the patients interviewed were familiar with the concept of tumour profiling and many demonstrated confusion around somatic and germline genetics. Cancer was generally perceived as being primarily hereditary, even by one highly educated patient who had a background in health communications:

> Generally as a lay person we are more inclined to look at family genetics. We would not think about, what you told me. When I say mutations, I was referring to the family genes you mention to me…I know every cancer cell is a mutation.. normally when we talk about mutations, we talk about family history (Patient 2)

Even though, as one clinician suggested, some patients were becoming more knowledgeable about somatic mutations and tumour development – possibly through their participation in clinical trials – it cannot be assumed that many patients recruited onto the POLARIS Discovery Profile will have this knowledge and experience. This finding was supported in the interviews with clinicians who agreed that patients would have limited understandings of genetics, mutations and cancer development. Some suggested that these limitations would even apply to clinicians who did not specialise in cancer genetics:

> "It is does not stop at patients. Even physicians. I've had so many…mis…even from physicians referring to me you can understand that their grasp of it is very low between driver and passenger mutations, between actionable and not actionable. So you can't blame patients for not knowing this. (Clinician 11).

Concerns about the knowledge and expertise of clinicians also surfaced in discussions about potentially incorporating germline testing into the POLARIS Discovery Profile. One clinician suggested that germline testing should be done as part the POLARIS Discovery Profile to provide participants with the most comprehensive information about their tumour. However, most of the clinicians interviewed were clear about their professional limitations and stated that they did not have sufficient training to counsel and educate patients about germline implications. In addition, some felt that routine germline testing along with tumour profiling would require a comprehensive multi-disciplinary team at Singhealth, which is still in its infancy. Clinicians were clear that a wider range of genetics specialists would be needed to counsel patients effectively:

> "Germline has implications for families. I am not trained; I am not comfortable to talk about germline mutations as it has implications for the rest of the family….. I will send you to a trained cancer genetics oncologist or counsellor or whatever to sort this out. It should not be done in my clinic. It has to be someone trained." (Clinician 1)

Given the conceptual complexity of gene mutations and tumour profiling, particularly for individuals not familiar with the biological sciences, the interviewer suggested that supplementary materials be provided to patients in addition to the formal participant information sheet. A pictorial brochure, adapted from the literature, was proposed to provide prospective participants with very general information about cancer genetics and the POLARIS Discovery Profile. An early draft of the brochure (shown in Appendix Eleven) was presented to patients and discussed during the interviews. Patients were generally supportive of the brochure and many said that the use of pictures helped to clarify the concepts, particular for individuals with limited English. However, it was unclear how effective the pictorial aids were in improving comprehension because, as the results above suggest, patient understanding of cancer genetics was limited even after the brochure was explained to them and the interviewer responded to their questions.

These results suggest that the consent process cannot solely rely on the provision of information and it cannot be assumed that patients will fully comprehend the participant information sheet without an in-depth explanation; even with the use of pictorial aids. Allocating time with patients to explain the research may help to overcome these limitations and improve participant comprehension of the Discover Profile and the implications of consenting to the storage and sharing of their biomolecular data. However, the time that would be required to explain the information in the consent documentation, and the

implications of participating in the Discovery Profile, may lead to another barrier depending on who is involved in this process. Involving clinical staff in the process of explaining the research to patients and taking their written consent may lead to resistance from clinicians.

Resistance from Clinicians

Two major issues were raised in relation to the role of clinicians in the consent process. First, there were concerns about the time that would be needed to explain the research adequately to patients during the consent-taking process. While the clinicians interviewed were generally comfortable about providing patients with written information about the Discover Profile and potentially taking the consent, there were also concerns about the how this process would impact on the volume of patients seen daily; especially if the information required thorough explanations and resulted in longer waiting times for other patients. As one clinician (9) put it, such an outcome would be "completely unethical". To compensate for the limited time, some clinicians suggested that a dedicated research officer or counsellor be available to explain the Discovery Profile in detail:

> "It may be better if someone else that is trained can do it… you just need a trained counsellor or a trained coordinator, research coordinator who is trained to explain it. And then obviously, we have to take the consent, we sort of don't have to go through the details of explaining. We just wrap up and answer any specific questions or concerns". (Clinician 1).

This idea was put to other clinician's interviewed and it was generally well-received as a way of minimising the time burden on oncologists, particularly those working in the public sector, and improving patient understandings of the research for which their consent was sought. The idea of a dedicated researcher being available to discuss the results of the Discovery Profile with patients was also discussed. While some clinicians agreed that a facilitator would be helpful, others felt that the responsibility to explain the results to participants should lie with the oncologist who has professional obligations to stay updated on current evidence of best practice:

> "They can provide additional information to assist the oncologists, but I think it is incumbent on the individual oncologist to know the information. Because at the end of the day they are physicians; it is their responsibility to keep up to date. Genomics is so much a part of oncology that you have to know". (Clinician 7)

The second issue that emerged in the interviews with clinicians was the cost of the POLARIS Tumour Profile test and its perceived conflation with the Discover Profile. Clinicians expressed concerns about patients paying out of pocket for the clinical test and this payment being perceived as subsidising the costs of the Discover Profile for POLARIS. Some clinicians felt very strongly that the costs of the clinical tests were unfair and should be free if the data were being used for research purposes; especially if revenue would be generated from the sharing of these

data other research institutions and the development of commercial products. Even though the interviewer stated repeatedly that service fees would only be charged for the clinically validated test, concerns around patients "paying for research" persisted:

> On the existing, existing variants and gene lines. That is already on a validated study so and if you are telling me that you are going to bring in research and get the patients to pay for research, I can categorically tell you not to. I am sure patients will not from my experience. (Clinician 4)

One clinician went as far to suggest that such a situation would be construed as coercive because the clinical settings may limit the perceived options of vulnerable patients to consent:

> "..you have to understand you have a group of patients who have just been diagnosed with cancer and you drop this bombshell that we can give you standard treatment or focused treatment but you have to pay a thousand dollars. I don't think consent in that situation is all the way fair…it is coercive scenario. They are under pressure, stress, family." (Clinician 9).

Only one patient interviewed enquired about the costs associated with clinical profile. This patient was told that the clinical test would be serviceable, but there would be no cost for the research. This observation suggests that patients may not have been aware that service fees would be charged for the clinical test. The patient expressed concern about rumours heard at the NCCS that patients were being asked to pay for research. More problematically, the patients interviewed might not have appreciated that the Discovery Profile was for research purposes only and not for their clinical benefit. If patients confuse the goals of the clinical profile with research participation, this may not only be perceived as a conflation of research and clinical care: it may also invite therapeutic misconception and lead to participants consenting to the Discovery Profile with the mistaken belief that the results will benefit their treatment.

Therapeutic Misconception

The suggestion that patients may mistakenly believe that the Discovery Profile will return clinically relevant findings to their treating clinicians was raised many times throughout the interviews despite patients being seemingly aware that the profile was for research purposes. As described previously, many patients preferred that Discovery Profile be returned to their treating oncologist for explanation on how the results might impact their cancer treatment, which may be indicative of therapeutic misconception. There was also evidence that patients might misconstrue the purpose of the Discover Profile in the interviews with clinicians who were concerned about the actions participants might take in response to the results and demands for unnecessary treatment. Some patients even stated that they would wish to consult a Traditional Chinese Medicine (TCM) physician about the results:

> "To have a clearer picture of what was done and also let us see if we go for Chinese TCM, we can bring this and show the Chinese physician and something supplement…a different kind of treatment. I think most cancer patients some of them go for Chinese medicine. Maybe they can complement—different way of treatment" (Patient 1).

Clinicians also felt that results from the Discovery Profile could potentially lead to the inappropriate provision of treatment without sound clinical evidence. Clinicians highlighted the fear that patients' experience after receiving a diagnosis of cancer and that participating in research could translate into hope that new treatments or explanations that cannot be provided. Indeed, some of these clinicians believed that results from the Discovery Profile could encourage a false sense of hope for how patients could benefit from participating in the research. In order to meet patient expectations, some were concerned that even without clinical evidence, the Discovery results could be acted upon unsolicited, and incur increased health care costs and unwarranted treatments:

> "I think, I envision that we will be very tempted to give treatment that is not standard based on those genes. Patient is desperate. It will be very tempting…. Let us imagine the patient has access to the 85 genes right…let's say that I, as the clinician, am going to stick to evidenced based medicine. And I am not going to treat your cancer based on some random mutation. There is no clinical trial available. All the patient does is to go off to a private oncologist, and says I have this mutation, give me this drug. It has implications moving forward, in terms of health care costs." (Clinician 1)

Other clinicians were less concerned about patients seeking second opinions from other healthcare professions and believed that patients would return to their treating oncologist for advice about the Discovery Profile. This setting may invite therapeutic misconception because it implies that patients might consent to the Discovery Profile on the advice of their oncologist in the belief that the results will inform their cancer treatment: especially if the oncologist who orders the clinical test also obtains written consent for the Discovery Profile. The expectations of both patients and clinicians in these settings must be carefully managed to ensure that participants do not confuse the goals of the two profiles or believe that participation will affect their treatment in any way. Because any perceptions of the consent process as coercive or conflating research with clinical care, would not only act as barrier for obtaining informed consent: they may also damage trusts relations with patients and the clinicians who treat them.

TRUST AS THE BASIS OF CONSENT

Trust is essential for all ethically justifiable research. The results thus far have indicated a number of challenges and barriers to obtaining informed consent for the POLARIS Discovery Profile, and for establishing and maintaining trust with participants. These results suggest that participants may misconstrue the research as being part of their clinical treatment, and will likely have very limited understandings of the somatic gene research they consent to. More

positively, however, the interviews were also indicative of ways that trust with participants and clinicians could be promoted to form the ethical basis of this research. Namely, the results suggest that participant's might consent to the Discovery Profile because they trust the regulatory systems and research institutions in Singapore to protect their personal information and share only de-identified data for purposes that might benefit future patients.

Privacy and Confidentiality

Protecting the privacy of participants and maintaining confidentiality was considered critical in the storage and sharing of the Discovery Profile. POLARIS aims to store not only the Discovery Profile for a period of ten years, but to share those data with researchers in Singapore and at international institutions. The possibility of sharing data with external researchers was discussed in the interviews with clinicians and patients. Both groups expressed the view that personal information had to be delinked from the stored data and not shared with third parties. Some clinicians also felt that the socio-political culture in Singapore would mean that few patients would be overly concerned about the storage and sharing of their Discovery results and would likely consent on the basis of assurances that that their personal data would be kept confidential in compliance with local laws and regulations:

> "I think we are just not so paranoid [laughs]. We are used to living under a totalitarian, maybe I shouldn't say that. Joking aside, most patients do not really care about privacy issues. All they can see if that their extra tissue is left aside is not my major personal data. They don't really care". (Clinician 3)

These cultural views were shared amongst some of the patients interviewed who felt that sufficient safeguards would be in place to protect privacy and prevent the data from being disclosed inappropriately and misused. Many patients seemed unconcerned about the systems that in place at POLARIS or other institutions to protect the data. Instead, they referred to the regulatory systems in Singapore – notably the PDPA and the HBR Act mentioned in the consent documentation – as providing reassurance against the possible misuse and disclosure of data. However, some patients were concerned about possible misuses, particularly with respect to the potential for discrimination:

> I am assuming that nothing will be released to a third party without my consent. If my tumour profile indicates something and that is then used to discriminate against me in a job or something then that can be horrible. Obviously other than that no (Patient 7);

Some clinicians also discussed the possibility of discrimination that could follow from germline analyses if included in the POLARIS Discovery Profile, and suggested that more legal protections should be in place before these types of tests are introduced into precision oncology. Specifically, one clinician mentioned that Singapore lacked the legal equivalent to the Genetic Information Nondisclosure Act (2008) in the United States that could prevent the results of

genetic tests from being used to discriminate against patients from obtaining employment or procuring adequate insurance. Hence, there were stated preferences for the Discovery Profile to not include analysis of genes that could imply germline mutations as this may change the perceptions of oncologists and undermine trust in the ability of institutions to protect participants from discrimination harms.

Altruism and Solidarity

Besides questions of possible harms, other issues emerged in the interviews around the direct and indirect benefits of participating in the POLARIS Discovery Profile. Some of the clinicians interviewed expressed concerns about the Discovery Profile data being shared globally with research institutions in other countries that lacked the accountability of publicly-funded institutions in Singapore. In these interviews, privately owned organisations were considered less trustworthy than government funded institutions, due to a perceived lack of oversight and transparency. Some clinicians felt that sharing participant data for profit-orientated research might create mistrust with oncologists and their patients. Indeed, one clinician perceived POLARIS as profit-orientated and having vested interests in the development of targeted therapies that few participants in the Discovery Profile, or patients like them, would benefit from due to the high costs of cancer treatment.

> I think POLARIS has to very careful as it doesn't want to come across as some big conglomerate that is trying to make money off patients. That is the big problem. There is already a feeling among a lot of patients on the ground that: you guys [meaning us] come up with new fangled medications and make it impossible for us to afford. (Clinician 9)

Perceptions of institutions as 'profit-orientated' and driven toward commercial development of products for private benefit conflicted with views of genome research as a 'public good'. These goods foster altruistic attitudes towards participation in research that potentially has wider societal benefits. These views about the beneficiaries of research were believed to fundamentally alter the institutional relationship with clinicians, who were unlikely to consider their role in the consent process for a profit-orientated databank as altruistic. That is, clinicians may expect to be paid to recruit patients onto the POLARIS Discovery Profile if the research is perceived as profit-orientated for private benefits; especially if additional time was needed in the clinic to explain the research and obtain the written consent.

On the other hand, the patients interviewed did not draw such distinctions between public and private goods although the possibility of commercial products being developed from the Discover Profile was not raised with these informants either. All patients interviewed indicated they would participate in the POLARIS Discovery Profile if offered to them and many appeared to understand that they would not benefit directly from participating. However, their willingness to allow their data to be stored and shared with other institutions was sometimes

premised on an understanding that the research was aimed at benefiting future cancer patients:

> "I feel very excited that someone can look at this and figure it out. And if they can figure it out here or in Argentina, I don't really care. It is going to be helpful to other people with a similar tumour profile I would actually be very interested in donating my tumour to science" (Patient 7)

These expressions of reciprocity and solidarity were indicative of attitudes that valued research as a public good for the benefit of cancer patients everywhere, and not just in Singapore. There were also indications amongst clinicians that patients would agree to participate in research altruistically if they believe it has the potential to benefit patients in future as a moral good:

> I think a lot of patients will do it for altruistic reasons.. most patients will do it. But I think they don't want to be made to feel as if they are guinea pigs. And so I think that's the balance you want to strike. I think you might want to say "Look whatever profits we get from these cell lines, we will donate it back to cancer". They don't feel as if they are being taken for granted and they are helping the future. (Clinician 9)

The reciprocation of indirect benefits back to the cancer community would be a strong moral justification for the POLARIS Discovery Profile. For many patients, cancer is a frightening experience; most patients interviewed in this study did not have a family history, many wanted to understand why they had developed cancer and were trying to make sense of their diagnosis. The possibility of having those questions answered through increased knowledge of the causes and pathology of cancer was highly valued, and patients could view themselves as contributing to that cause as a benefit. Trust in the potential of the POLARIS Discovery Prolife to generate further knowledge around cancer causation may provide the strongest moral justification consenting participants for the research.

DISCUSSION AND RECOMMENDATIONS

The proposal to launch a precision oncology clinical service in Singapore with concurrent research participation is opportunistic and valuable for the improvement of treatment focused intervention locally. However, clarity around the purpose and boundaries of clinical and research domains is essential to avoid conflation and minimise confusion, particularly when both are conducted by the same provider. For this approach to be effective, careful consideration to the consent process is essential. As the integration of NGS to inform patient care is only recent in oncology practice, this is experience is novel to researchers, clinicians, and especially to patients. Therefore, developing a framework for obtaining consent from participants for this type of research becomes challenging when recommendations specific to tumour profiling worldwide are limited and there are no best practice principles explicit to genomic research in a Singaporean context.

A framework for obtaining informed consent to store and share the POLARIS Discovery Profile was thus developed by drawing on international literature on obtaining informed consent specific to genomics research and biobanks. Recommendations made for this framework are also informed by the results of the qualitative interviews with the service users (oncology healthcare professionals) and the target population (oncology patients) in a local healthcare setting. In addition, the POLARIS Discovery consent form was then critiqued by international and local bioethicists (refer to Appendix Twelve for overview of consent form and process data collection). In this chapter, these results are discussed with reference to the extant literature to make recommendations for a consent process that is grounded in principles of trust and respect for participants who take part in the POLARIS Discovery Profile. Recommendations are also made in relation to the return of individual research results and incidental findings.

THE PROCESS OF INFORMED CONSENT

Informed consent for human subject research is not an event that takes place once after prospective participants are given information about the study and sign the written consent form. According to principles set out in the GA4GH (2015) Consent Policy, “consent is an open, communicative and, ideally, continuing relationship” that starts at the time prospective participants are initially approached to take part and continues over the lifetime of the databank, or until the participant withdraws their consent. Maintaining such an enduring relationship requires commitments from research institutions that go beyond the mere provision of information and written consent; they must also adopt policies and implement strategies that promote trust with research participants (O'Neill 2002) and allow for the storage and sharing of genomic data within ethically acceptable parameters. Based on the results of the present study, recommendations are made on the preferred model of consent, the nature

of the information to be included in the formal consent documentation, and the options for sharing data and withdrawal the POLARIS Discovery Profile, as well as the appointment of a dedicated research co-ordinator.

Recommended Model of Consent

Results from the present study suggest that clinicians and participants in the POLARIS Discovery Profile would prefer a simple model where consent is given just once. The clinicians interviewed preferred this model because they lacked the time needed to explain adequately the implications of multiple consent options. Some also felt that participants would not fully comprehend different categories of research and would be happy to provide a one-off consent. This view corresponded with those of patients who were generally unconcerned about consenting to their tumour profiling data being stored at POLARIS with their personal information providing that the data were only shared with external researchers in a de-identified format, and in compliance with Singapore laws and regulations.

These preferences could imply either broad or blanket models of consent, although the issue of whether IRB approval should be required for specific projects was not explicitly discussed in the interviews. While both models have been criticised in the literature for providing insufficient information to participants and breaching individual autonomy (Caulfield 2009; Hoffman 2009), broad consent regiments have generally been adopted as standard international practice (Allen and Foulkes 2011). Scholars have also argued that broad consent is ethically defensible based on the public good of these facilities (Hansson et al 2006) and the added protections that the IRB system can provide to participants. This model would also be most consistent with the PDPA (2013) and HBRA (2015), which stipulate that participants must consent to the storage of identifiable data and that an IRB must approve specific research projects to access those data. A blanket model, which does not require IRB approval for specific projects, may not be legally compliant in this context. Therefore, a broad consent regiment is recommended for the POLARIS Discovery Profile.

- **<u>Recommendation 1</u>: The POLARIS Discovery Profile should be implemented using a broad consent regiment.**

Implicit to the model of broad consent is the nature and scope of information that is presented to participants during the consent process. While traditionally, the view has been to provide prospective participants with comprehensive information about the research, its goals, and the risks and benefits of participating. However, reported evidence of limited comprehension amongst participants in genome research of genomics and cancer genetics (Lea et al. 2011; Kaphingst et al. 2012; McGowan et al. 2014; Gray et al. 2012) has prompted some scholars to argue that information should be provided in a clear and simplified format (Beskow et al. 2010).

Others propose tiering information according to its relative importance, such that all participants receive essential information about the research, while others may opt to access additional supplementary information about genomic databases and potential research applications (Bradbury et al. 2014).

Results of the present study support the use of simplified documentation with supplementary information. Similar to reports in the prior research, the patients interviewed in this study had very limited understandings of cancer genetics and tumour profiling. As elsewhere, participants were confused about the differences between somatic and germline profiling, and the concept of informed consent appeared foreign to many despite having considerable time to review the documentation and ask questions of the researcher. This experience was corroborated in the interviews with clinicians who felt that participants generally would not expect to receive comprehensive information about the research to give their consent. Clinicians also preferred simplified documentation because of the limited time they had to adequately explain detailed, scientific information about the POLARIS Discovery Profile.

While the results indicate that clinicians would not wish to spend excessive time explaining these details, there was support for participants being given supplementary information with simple explanations of tumour profiling, genetic mutations and the Discovery Profile. While the patients interviewed were generally able to read and speak English, their ability to comprehend complex scientific concepts in English appeared far more limited. Thus, pictorial aids with graphic illustrations were introduced as tools that are commonly deployed in science communications to help overcome language barriers. Including graphic illustrations of cancer genetics and tumour profiling in supplementary information may help to improve participant understandings of these concepts and promote a more informed consent. Therefore, a simplified approach is recommended for the POLARIS Discovery Profile in addition to the provision of supplementary information with pictorial aids.

- **<u>Recommendation 2</u>: The POLARIS Discovery Profile should be implemented using simplified documentation with optional supplementary information and translated into the official languages of Singapore.**

Information to be included in the formal documentation (i.e. participant information sheet and written consent form) was initially extracted from the literature that outlined the minimal requirements needed to obtain consent for sharing and storing genomic data: i.e. the purpose of study, costs of participating, privacy protections, storage parameters, collection of personal information and medical records access (Beskow and Dean 2008; Wolf et al, 2012; Beskow et al 2010). Other literature provided guidance on simplifying the form and structure of the documentation (McGuire and Beskow 2010; Allen et al 2011; Ayuso et al; 2013; Lolkema et al 2013; Bradbury et al 2014) and was incorporated into the initial draft that was discussed with

patients and clinicians interviewed in this study (see Appendix Eight). It was generally agreed that the information provided in this documentation was sufficient for participants to give consent for the POLARIS Discovery Profile.

Data Sharing and Withdrawal Options

The initial documentation also included options for the sharing of Discovery Profile data and withdrawing from the research. Language describing the sharing of data and establishment of data protections mechanisms was incorporated from the GA4GH Consent Policy (2015). According to principle (iv) of this Policy;

> Data donors have a right to not participate in international data sharing or, if participating, are able to withdraw, with the understanding that it may not be possible to retrieve and/or destroy data once shared.

This principle was interpreted as giving participants the option of consenting to store their profile data for research within the local jurisdiction whilst opting out of those data being shared with researchers internationally. However, this option was removed from the recommended consent documentation (shown in Appendix Thirteen) primarily because the results suggest that participants who consent to the POLARIS Discovery Profile would be unlikely to opt out of their data being shared with international researchers. As discussed previously, the patients interviewed were generally supportive of the Discovery Profile and would likely consent to their de-identified data being shared with international researchers providing that they complied with Singapore laws and regulations.

Furthermore, the option introduces unnecessary complexity into a process that has been simplified according to the preferences of the primary stakeholders in this research, and in compliance with local laws and regulations. The HBRA (2015) does not stipulate any legal requirements for participants to be given an explicit option to share their data with researchers outside of Singapore, although it does require that participants be informed of these possibilities prior to consenting. The law also requires that participants be given the option to withdraw from any research that is linked to personally identifiable information. Even though our results suggest that participants in the POLARIS Discovery Profile would be unlikely to withdraw from the research, compliance with this law would mandate that any personally identifiable data be deleted upon the withdrawal of a participant's consent. Thus, this information is included in the recommended consent documentation.

Once a participant has consented to the POLARIS Discovery Profile, a complete withdrawal will be limited once the de-identified data has been shared with an external institution. The practical difficulties of retrieving data once it has been de-identified, and shared with other researchers, is a recognised limitation to withdrawing fully from large-scale genomic databases

(Lunshof et al., 2012). From a legal perspective, research with de-identified data is not regulated under the HBRA (2015) or any other regulatory instrument in Singapore. Therefore, providing that participants are made aware of this limitation prior to giving their consent for the Discovery Profile it may be justified ethically and legally to limit the withdrawal options to the deletion of any information linked to the participant that is stored at POLARIS. Information about participant options to withdraw, and their limitations, is also included in the recommended consent documentation.

Return of Research Results and Incidental Findings

The obligation to return research results and incidental findings to patients in genetics research is contested and currently lacks consensus (Zawati and Knoppers 2012). Some scholars argue that that researchers have a moral duty to return research results (Belsky and Richardson 2004; Richardson 2008) and that patients have rights to access those data (Caulfield et al. 2008). Others argue that it fails to benefit patients when the findings are not clinically valid or actionable (Androno, 2004; Wolf et al 2012; Zawati and Knoppers 2012), and the promise of returning results risks inviting therapeutic misconception (Zawati and Knoppers 2012). Others acknowledge that some participants would prefer not to know adverse findings and advocate that policies for returning results should be considered in the context of institutional and culturally acceptable practices and laws (Beskow and Burke 2010). In Singapore, there are no laws that create legal duties for researchers to return results or incidental findings to participants; nor are there any explicit rights 'not to know'.

Results from this study suggest that participants should be given the option to receive the results of the POLARIS Discovery Profile, and be made aware of the potential for incidental findings during the consent process. Both clinicians and patients interviewed were largely supportive of participants being given this option. While there is not legal or moral obligation for POLARIS to return the Discovery Profile report, the costs of doing so will not be high and it may be considered a sign of respect to the participants who altruistically consent to their data being stored and shared for research purposes. Therefore, information should be provided to prospective participants on the option to receive the Discover Profile prior to giving their consent. Results should be also returned with a detailed explanation from someone qualified to interpret the results and clearly explain that they will have no relevance or utility for their current clinical care (Burke et al. 2014).

There was less support, however, for participants being recontacted with future relevant research results; for example, in the event that new gene variants become clinically actionable but were not been included in the POLARIS Discovery Profile consent form. Some clinicians interviewed thought that the logistics of recontacting participants would be too complicated,

and patients felt that the ten-year period in which the Discovery Prolife would be stored was too long for them to benefit from a future recontact. In addition, patients are unlikely to benefit from being recontacted since the clinical relevance of variants are pertinent only to cancer treatment at the time of diagnosis. Thus, an option for patients to be re-contacted in future should not be included in the consent process.

- **Recommendation 3: The POLARIS Discovery Profile consent process should include the option of returning the report to participants but not for recontacting them with future research results.**

The return of incidental findings was more complex. The inclusion of genes on the POLARIS Discovery Profile that have additional germline implications, such as BRCA and TP53, has been contentious. Data collected on the occurrence of somatic variants in these genes is significant for new cancer treatments, although if these variants are of germline origin, they can also infer susceptibility to an inherited genetic syndrome. While one clinician interviewed suggested that POLARIS remove those genes with germline implications from the Discovery Profile prior to returning results to participants, most clinicians and patients were generally comfortable with the inclusion of these genes providing that they were accompanied with an adequate explanation when the results are issued. In recommendations for the delivery of tumour profiling results, Raymond et al. (2016) suggests that oncologists draw on the expertise of genetics specialists to assist with the interpretation and discussions of those findings with participants. The possibility of incidental germline findings and genetic discrimination also emerged from interview data. There are currently no laws in Singapore to protect patients against employment and insurance discrimination due to their genetic status. As a result, germline genetic findings do have the potential to adversely impact on health coverage; particularly through the public health insurance scheme in Singapore, Medishield Life (2015). This policy enables medical records from Singaporean medical institutions to be accessed by authorised representatives. However, findings from the Discovery Profile are still considered as research and would have to be clinically validated to verify any germline implications that could have an impact on participant's health insurance. Therefore, acknowledging that incidental findings may be revealed with the return of the Discovery Profile is recommended along with ensuring that participants can be referred to relevant specialists to validate the findings and take action where appropriate.

- **Recommendation 4: Incidental findings from the POLARIS Discovery Profile should be acknowledged when individual results are disclosed and participants referred to clinical specialists as appropriate.**

In a recent study, it was found that the collection of tumour-only samples to identify somatic mutations leads to false-positive findings because they cannot be distinguished from germline

variants (Jones et al. 2015). The authors of that study have recommended that tumour profiling be performed in combination of a germline sample for precise clinical management. Given these findings, POLARIS could adapt the assay to incorporate germline analysis in the future. The prospect of germline sample collection and management of secondary findings was explored with clinicians in the interviews, who were generally very aware of their professional boundaries and that the resulting implications (beyond patient treatment) would require the inclusion of genetics specialists and ideally input from a robust multi-disciplinary team. Although such models of care are available in other countries, such as the U.S., UK and Australia, it was acknowledged that readily available access to genetics services in Singapore is still in progress and would require substantial institutional developments. In situations where research involves germline tissue testing, it is clear that the consent process for tumour profiling will need to be re-examined and substantially modified to incorporate these considerations.

Support of a Research Co-ordinator

A final recommendation for the consent process is made for the support of an independent research co-ordinator. This recommendation came from the results as a strategy to lessen the time-burdens on clinicians involved in the consent process, to enhance participant comprehension of the POLARIS Discovery Profile, and to engage them directly in a relationship of trust and mutual understanding. As discussed previously, it was evident from the patient interviews that participant understanding of informed consent and tumour development would be very limited amongst the patients interviewed. These limitations are not limited to Singapore, (i.e. Beskow et al. 2010; Lea et al. 2011; Kaphingst et al. 2012; McGowan et al. 2014; Gray et al. 2012) but are complicated by the multi-lingual context and cultural beliefs within local healthcare settings that may contribute to the varied understandings of genes and inheritance in cancer development (Lim, 2005).

Clinicians interviewed in this study stated that they often lacked the time to explain medical protocols and outcomes in detail with their patients, and indicated that would they would not have time to provide lengthy explanations of the POLARIS Discovery Profile. This reality of the local healthcare setting suggests that additional resources would be required to support the consent process. Dedicated research co-ordinators are frequently appointed to support the recruitment and consent process for research. In the context of genomic research, some scholars have recommended the appointment of trained genetic counsellors to deliver the consent documentation and explain to participants the implications of consenting (Kaphingst et al. 2012, Levenseller et al. 2014). However, the expertise of a genetic counsellor may not be necessary or appropriate for the POLARIS Discovery Profile, as the main focus is on somatic mutations and will only generate implied germline implications.

The results of this study indicate that participants would prefer an individual who suitably qualified to explain the research and any results that are returned, although they would not necessarily need to be trained in genetic counselling. With a few exceptions, the clinicians were generally supportive of a dedicated research co-ordinator being available to explain the consent documentation in detail and take the written consent from participants. Many patients interviewed indicated their preference for an oncologist to deliver this information, although they would also accept an independent researcher. The only personnel patients were averse to discussing this information with were the nursing staff out of concern that they lacked the necessary expertise to address their questions fully. Therefore, the appointment of a dedicated research co-ordinator is recommended to support the consent process.

- **<u>Recommendation 5:</u> The POLARIS Discovery Profile should be implemented with the support of a dedicated research co-ordinator.**

In addition to providing a supportive role throughout the consent-taking process, a dedicated research co-ordinator would have additional benefits in helping to maintain a clearer distinction between the POLARIS Discovery Profile and the clinically validated test that patients' access for their cancer treatment. This distinction is important to avoid conflating the research with the patient's clinical care. Having a research co-ordinator available to explain the distinction thoroughly will help to minimise therapeutic misconception. In addition to reducing these misconceptions at the time when consent is taken, assigning a dedicated research co-ordinator to return individual results and incidental findings from the Discovery Profile may also help to clarify the distinction further and reduce participant misconceptions about the benefits of the research. The role of the research co-ordinator in the recommended consent process is shown in Appendices Fourteen and Fifteen and the final draft of the consent form, which has been crosschecked with provisions in the PDPA (2012) and HBRA (2015), is included in Appendix Thirteen.

PROMOTING TRUST RELATIONS BETWEEN CLINICANS AND PATIENTS

From the results of this study, it is clear that the storage and sharing of tumour profiling data cannot be ethically justified as an exercise of personal autonomy when the informed consent of participants is inherently limited. Even with the support of dedicated research staff and a simplified consent process, the degree to which participants on the POLARIS Discovery Profile can be truly informed of the implications for consenting to the storage and sharing of these data with researchers in Singapore and abroad is uncertain. Thus, it is important to ensure that other measures are in place to protect participants from unnecessary harms and that their data is shared within the morally accepted parameters of the consent. In short, participants must be able to trust that their data will be protected and used for the purposes they consented to.

The integration of the POLARIS Discovery Profile into oncology clinical practice was generally accepted by both clinicians and patients interviewed in this study; clinicians were open to assist in recruitment and patients were willing to participate. However, the clinicians expressed concerns about how participant's data would be shared with other institutions and for what purposes, who benefits from the use of these data, and the transparency around this use. When the cost of the POLARIS Tumour Profile was raised, there was some confusion amongst the clinicians about the patients having out of pocket for the clinical test while their data would be utilised for research. Furthermore, some clinicians perceived POLARIS to be a for-profit commercial entity exploiting vulnerable patient populations. Although POLARIS is government funded, this perception may have arisen because the laboratory is not situated in a public hospital. Regardless of where these concerns originate from, if clinicians do not believe POLARIS to be trustworthy, then it is likely that participants will not either.

A lack of trust with clinicians and patients would have significant implications for the value of POLARIS as a biomolecular databank specific to the health needs of the Singaporean population. Storage and sharing these data with external researchers will be key to fostering research and ensuring the widest public health benefits (Knoppers et al. 2011). The potential for these benefits justifies the enormous public resources that are invested in genomic databanks and their purpose as a public good. Maintaining trust in this public good not only requires security measures to protect the data of participants, but will also require transparency in how the data are accessed and benefits are distributed (Caulfield et al. 2008). Any intention to privatise these benefits should be disclosed to participants prior to consenting and policies should be in place to restrict access to the data for purposes participants have consented to.

The results of this study support the adoption of a broad consent model where participants would not consent to specific projects or types of research. However, they also suggest that participants would consent altruistically on the condition that their data is used for research that has the potential to benefit other cancer patients in the future. This finding is supported in the literature with other evidence that solidarity with future patients incentivises participation in research that is unlikely to have direct benefits for participants (Felt et al. 2009). The solidarity principle forms the basis of ethical arguments that justify the use of broad consent regiments for genomic research (Knoppers and Chadwick 2005), but the acceptability of this approach is also attached with provisions for governance mechanisms that ensure transparency and accountability in how data are stored and shared with other researchers and institutions. Such mechanisms may include approval from an IRB for specific projects, or a separate independent body comprised of members with relevant expertise to provide oversight for the release of data to external institutions and the distribution of benefits (Caulfield et al. 2008). These oversight structures are recommended for the POLARIS Discovery programme.

- **<u>Recommendation 6:</u> POLARIS should adopt governance structures and policies that ensure transparency and accountability in the storage and sharing of Discovery Profile data.**

In establishing a policy for the release of the Discovery Profile data to external institutions, it is important to understand what research participants would likely consent to if they were asked. While the results of this study indicate that participants would consent to the data being shared for the purposes of cancer research, this might not be limited to cancer research only as other types of biomedical research were not discussed in the interviews. However, the consent might not extend to non-medical related research, such as military research or forensic investigations. Concerns over the use of genetic data for these purposes has been raised in the literature (O'Niell 2002; Hoffman 2009), and while they are most relevant to germline research rather than somatic tumour profiling, participants are unlikely to understand these differences well enough to assume that they appreciate the risks of sharing these data. In these circumstances, institutions must assume a guardianship role to ensure that the data entrusted to them is not misused or perceived as such.

Finally, the concept of benefit sharing is another principle that has emerged to justify the use of broad consent regiments for genome research (Knoppers and Chadwick 2005). This principle does not imply that participants should benefit directly, as it is important not to promote therapeutic misconception. Rather, the principle prioritises benefits to be shared with *communities*. In the context of this study, the principle implies that mechanisms should be in place for the expedient dissemination of published research results as new discoveries in cancer treatments emerge and the reclassification of variants becomes clinically significant. Results of this study suggest that POLARIS could share these benefits through the provision of professional education sessions at the NCCS or establishing open electronic platforms where oncologists could have rapid access to emerging scientific and clinical developments. The development of platforms that enable the effective communication with clinicians on research outcomes is recommended for POLARIS.

- **<u>Recommendation 7:</u> POLARIS should develop platforms to communicate effectively with clinicians on research findings generated from the Discovery Profile data.**

Such platforms could include lunchtime seminars, open access databases or other communication materials. These initiatives would help to maintain a dialogue between oncologists and POLARIS to ensure that the research emerging from the tumour profiling data are directed back into clinical practice. Education sessions could also assist build clinician confidence so that the role of genetics and genomics can be incorporated into their patient discussions. In addition, they would form part of a long-term initiative of relationship building that would promote trust with clinicians and the patient communities they care for.

CONCLUSION

From international resources there is a multitude of research, opinions and recommendations that can be drawn on to guide informed consent for biobanking and genomic research. This literature was essential in developing the framework for precision oncology testing and research consent. However, the findings from this exploratory study gave a unique insight into the views and preferences of clinicians and patients, which collectively modelled the informed consent process pertinent to the practicalities of a Singaporean hospital.

This study has highlighted that there is limited public awareness around cancer causation and genetics as well as an understanding of what informed consent entails. As genomics advances, communication of these concepts will become increasingly complicated. The engagement of a POLARIS research co-ordinator is strongly advocated to overcome the barriers identified from this study in obtaining informed consent. The role of the research co-ordinator includes: assisting with recruitment; clarifying participation of research; explaining results and being a point of contact for any new developments; developing supportive material to increase patient comprehension; leading in professional education such as workshops. The findings from this research study have also informed the development of the consent form and workflow. These documents and the involvement of a research co-ordinator are advances in ensuring that informed consent can be obtained in precision oncology settings in Singapore.

LIMITATIONS AND FUTURE DIRECTIONS

This study has a number of limitations, which should be considered in interpreting the results. While clinician data became saturated at 11 interviews, the response rate of 14.8% is rather small for qualitative research. It is unclear if systematic differences exist between those agreeing to participate and those not, creating selection bias. The small response rate does raise possibilities of potentially differing opinions on the part of those not participating. Even though the response rate was small, the views of the stakeholders are reflected in the literature on the type of consent model, how the consent should be taken, returning of results and data protection mechanisms.

The current POLARIS Tumour Profile Test and POLARIS Discovery Profile are targeted to GIST cancer patient; due to unforseen circumstances at the National Cancer Centre, interviews could only be conducted with breast cancer patients. Therefore, the demographics are heavily skewed towards female patients and data are from a patient cohort that will not immediately benefit from the test. It is unclear if males would have different opinions from female patients about participating in tumour profile research, storage and sharing of tumour profile data and return of results.

Numerous areas of research have been identified to expand the scope of data collection and evaluate the process of integrating tumour profiling into clinical practice. These include:

- Increasing participant cohort to GIST cancer clinics who are targeted to the current POLARIS Tumour Profile test with the inclusion of male perspectives
- Developing patient brochure to simplify the tumour profiling process
- Collecting data from additional tertiary Singaporean hospital such as National University Cancer Centre
- Interviewing patients who have had germline genomic testing about their views of incidental findings
- Evaluating the experience of clinicians and patients after the POLAIRS Discovery Profile has been launched in a clinical setting

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APPENDICES

APPENDIX ONE: LIST OF 93 GENES COMPRISING THE POLARIS CANCER PANEL

ACVR2A	DCC	FGFR1	MAP2K1	NRAS	SDHB	TYMS
AKT1	DPYD	FGFR2	MAP2K4	PDGFRA	SDHC	UGT1A1
ALK	EGFR	FGFR3	MDM2	PIK3CA	SDHD	VEGFA
APC	EP300	FGFR4	MET	PIK3R1	SETD2	
ARID1A	ERBB2	FLT1	MLH1	PMS2	SLC9A9	
ATM	ERBB3	FZD3	MLL	POLE	SLCO1B1	
BCL2L11	ERBB4	GLI3	MLL2	PTEN	SLCO1B3	
BRAF	ERCC1	GNAS	MLL3	PTGS2	SMAD2	
BRCA1	ERCC2	HRAS	MSH2	RAF1	SMAD4	
BRCA2	EXO1	IGF1	MSH3	RB1	SOX9	
CDH11	FAM123B	IGF1R	MSH6	RET	STK11	
CDKN2A	FAT4	KDR	MTHFR	ROS1	TCF7L2	
CDX2	FBXW7	KIT	MUTYH	RSPO2	TGFBR2	
CREBBP	FCGR2A	KLF5	MYC	RSPO3	TIAM1	
CTNNB1	FCGR3A	KRAS	MYH11	SDHA	TP53	

APPENDIX TWO: INHERITED PREDISPOSITION GENES INCLUDED IN POLARIS CANCER PANEL

Genes associated with inherited colon cancer
APC - Familial adenomatous polyposis
MLH1 - Lynch syndrome
MSH2 - Lynch syndrome
MSH6 - Lynch syndrome
PMS2 - Lynch syndrome
MYH (*MUTYH*) - MYH-associated polyposis
PTEN - Cowden syndrome
STK11 - Peutz-Jeghers syndrome

Genes unrelated to inherited colon cancer
BRCA1 – breast, ovarian cancer + others
BRCA2 – breast, ovarian, prostate, pancreatic cancer + others
MYH11 – Marfan syndrome, Loeys-Dietz syndrome
RB1 - Retinoblastoma
RET - Hirschsprung disease, Multiple endocrine neoplasia type 2
SDHA - Leigh syndrome, Paraganglioma
SDHB - paraganglioma, pheochromocytoma
SDHC - paraganglioma, pheochromocytoma, gastrointestinal stromal tumors (GISTs)
SDHD - Carney-Stratakis syndrome, paraganglioma with GIST or renal cell cancer
TGFBR2 - Loeys-Dietz syndrome
TP53 - Li-Fraumeni syndrome

APPENDIX THREE: STAKEHOLDER INVITATION EMAIL.

This email, amended to reflect the names of stakeholders, will be sent to inquire about the interviews.

Dear [insert name]

You are invited to participate in a research study. This purpose of this study is to develop the informed consent process and documentation for the POLARIS Cancel Panel Test. This test will be ready for clinical application in late 2015/early 2016. POLARIS is an A*Star funded initiative developing personalised medicine to improve diagnosis, treatment and health care outcomes in Singapore. We are interested in your viewpoints of the informed consent process for genomic testing. We hope you are able to participate and contribute your insights to further genomic testing in Singapore and the wider region.

This study has been approved by the Singhealth IRB [insert approval number] and is a collaboration between Singhealth, A*Star and the Centre for Biomedical Ethics at NUS School of Medicine.

The interview will take not more than one hour and can be held at a date and time convenient to you; it can also be conducted on the phone. Please review the attached information sheet and consent form for this study. Do not hesitate to contact me with any questions or comments. If you agree to participate in this study, please email your consent to Jyothi Thrivikraman at thrivijk@gis.a-star.edu.sg. If your interview will be conducted face to face, I will seek written consent before the interview commences. If we are speaking on the phone, emailed consent will suffice.

I look forward to hearing from you regarding study participation. I will also follow up via email in case I do not hear from you within a week.

Thank you very much for your time.

With best regards,

Jyothi Thrivikraman, PhD
Post Doctoral Fellow
Genome Institute of Singapore
60 Biopolis Street, Genome, Singapore 138672
Ph: +65 6808 8207; Email: thrivijk@gis.a-star.edu.sg

APPENDIX FOUR: CLINICAN INFORMATION SHEET AND INTERVIEW CONSENT FORM

Project Title: *Developing the Informed Consent Procedures for Molecular Profiling in Singapore*

Principal Investigator and Contact Details

Dr. Patrick Tan
Senior Group Leader, Genome Institute of Singapore
Principal Investigator (Adjunct),National Cancer Centre, Singapore
Phone: +65 68088053
Email: chuah2@gis.a-star.edu.sg

What is the purpose of this research?

You are invited to take part in a research study to gain insights on how molecular profile testing may be implemented within local healthcare systems in Singapore. This study is part of a larger project at the Genome Institute of Singapore (GIS) called POLARIS. POLARIS is an A*Star funded initiative developing personalised medicine to improve diagnosis, treatment and health care outcomes in Singapore. The POLARIS cancer panel test will identify the molecular profile of tumours for treatment purposes however will also analyse additional genes for research. The testing will be performed within the POLARIS laboratory at the Genomic Institute of Singapore and serve the local population. With the informed consent of patients, the molecular data from the tumour analysis will be stored with POLARIS for future study by researchers in Singapore and globally. An informed consent process that is culturally-sensitive to local norms and preferences, and validated according to local healthcare settings will be critical for the gathering, storage and sharing of genetic data for clinical and research purposes. We need your input in helping us design the informed consent procedures for this test.

Who can participate in the research?

You were referred by a member of the study team as a key stakeholder to help establish the informed consent process for the POLARIS cancer panel test. We are looking to interview oncologists, nurses, genetic counselors, IRB members at Singhealth. Upon completion of the interview, we will ask for your recommendations on other key stakeholders to interview.

What is the approximate number of participants involved?

We hope to interview between 10 to 15 stakeholders amongst the range of health care professionals indicated above in both Phase 1 and Phase 2.

What will my participation involve?

You will be asked to participate in interviews each lasting about one hour. For the exploratory phase (Phase 1), we will seek your input on how the cancer panel test can be incorporated into clinical practice, including delivery of informed consent. Other areas for discussion will be return of incidental findings, model of informed consent, storage and sharing of data

You are also invited to participate in a second round of interviews (Phase 2). For this second round, you will be asked to validate the patient information sheet and informed consent procedures developed in consultation with stakeholders and patients from Phase 1.

The research period is from July 2015 to December 2015.

How will my privacy and the confidentiality of my research records be protected?

Only the interviewer will have access to identifiable data (e.g. names and contact information) from the interviews. This information will not be released to any other person, including other members of the project team given that you are colleagues of the investigators. Identifiable information will never be used in a publication or presentation. All interview responses will be transcribed without identifiable information (i.e. only identified with a passkey). Interviews will be audio-recorded and de-identified during transcription for analysis. De-identified data will be stored according to NUS/GIS Research Data Management Policy to ensure confidentiality and protect the privacy of participants. Only the research team will have access to the de-identified data, which will be analyzed using thematic and content analysis techniques to identify common themes. Research data used in publication will be kept for a minimum of 10 years before being discarded. The coded data will not be used for future research, nor will participants be contacted for future studies.

What are the possible discomforts and risks for participants?

This research involves minimal risks and participants should not experience any physical discomforts. To minimize any identification of data, stringent data security measures have been established. Only the interviewer will have access to identifiable data.

Will there be reimbursement for participation?

You will not be reimbursed or financially compensated for your participation.

What are the possible benefits to me and to others?

There is no direct benefit to you by participating in this research. You will, however, contribute to developing the informed consent process for tumour testing in Singapore.

Can I refuse to participate in this research?

Yes, you can. Your decision to participate in this research is voluntary and completely up to you. You can also withdraw from the research at any time without giving any reasons, by informing the principal investigator and any data collected will be discarded.

Whom should I call if I have any questions or problems?

Please contact Jyothi Thrivikraman at **+65 68088207** and **thrivijk@gis.a-star.edu.sg** for all research-related matters and in the event of research-related injuries. This study has been reviewed by the SingHealth Centralised Institutional Review Board for ethics approval. If you have questions about your rights as a participant, you can call the SingHealth Centralised Institutional Review Board at 6323 7515 during office hours (8:30 am to 5:30pm). If you have any complaints about this research study, you may contact the Principal Investigator or the SingHealth Centralised Institutional Review Board.

Consent Form

Project Title: *Developing the Informed Consent Procedures for Molecular Profiling in Singapore*

Principal Investigator:

Dr. Patrick Tan
Senior Group Leader, Infectious Disease, Genome Institute of Singapore
Principal Investigator (Adjunct),National Cancer Centre, Singapore
Phone: +65 68088053
Email: chuah2@gis.a-star.edu.sg

I hereby acknowledge that:

1. I have read the participant information sheet that explains my role in this research.
2. I have had the opportunity to ask questions and am satisfied with the explanation and answers to my questions.
3. I agree to the audio-recording of my interviews.
4. I agree to the storage of audio-recording which will be de-identified.
5. I understand I can withdraw from the research at any point of time by informing the Principal Investigator and all my data will be discarded.
6. I understand that Phase 2 interviews will take place an as yet unspecified time, but before December 2015. I also understand that I do not need to participate in Phase 2 interviews and can decline

Consent Declaration

Phase 1 exploratory interviews	**Phase 2 descriptive interviews**
☐ agree	☐ agree
☐ do not agree	☐ do not agree

7. I give permission for researchers to contact me via mobile phone / email (*circle preferred method*). I understand that researchers will attempt to contact me up to three times using my preferred method of communication for Phase 2.

Participant's Name: _____

Participant's Signature: _____

Date: _____

Email: _____ Telephone Number: _____

Statement by the person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the study procedures and process. I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this information sheet and consent has been provided to the participant.

Print Name of person taking the consent_____

Signature of person taking the consent_____

Date _____

APPENDIX FIVE: PATIENT INFORMATION SHEET AND INTERVIEW CONSENT FORM

Project Title: *Developing the Informed Consent Procedures for Molecular Profiling in Singapore*

Principal Investigator and Contact Details

Dr. Patrick Tan
Senior Group Leader, Genome Institute of Singapore
Principal Investigator (Adjunct), National Cancer Centre, Singapore
Phone: +65 68088053
Email: chuah2@gis.a-star.edu.sg

What is the purpose of this research?

You are invited to take part in a research study that is interested in your understandings and thoughts on genetic testing of tumours for treatment and research. This study is part of a larger project at the Genome Institute of Singapore (GIS) called POLARIS. POLARIS is an A*Star funded initiative developing personalised medicine to improve diagnosis, treatment and health care outcomes in Singapore. Personalised medicine means treatment tailored for your specific health condition and genetic profile. The POLARIS cancer panel test will be able to identify genetic mutations for certain cancers to improve your treatment, but also analyse additional genes from your tumour for research. Before the test is offered at the National Cancer Centre, researchers need to ensure that patients understand the purpose of the test and how the genetic data will be used. This is called "informed consent". We value your input in helping us design these informed consent documents.

Who can participate in the research?

We are looking for women and men between the ages of 21 and 70 years of age who have breast, colon or lung cancer requiring chemotherapy. You also must speak English as the interviews will be conducted in English. Phase 1 of the study, interviews with Singhealth professionals, has been completed. Their input helped us to develop the documents we are asking you to review and validate.

What is the approximate number of participants involved?

We are asking for input from up to 10 patients at the National Cancer Centre who have not participated in the research already.

What will be done if I take part in this research?

You will be asked to participate in an interview of up to one hour. The interview will be conducted one to one in a private room at the National Cancer Centre at a time convenient for you. You will be asked to review the patient information sheet and informed consent document and then asked a few questions about your understanding of what will happen with your genetic data. You will also have the opportunity to ask questions about the material you have read. All interviews will be audio-recorded and transcribed and the data will be de-identified. The next section will detail how your information will be kept confidential.

How will my privacy and the confidentiality of my research records be protected?

Only the interviewer will have access to your identifiable information (e.g. names and contact information). This information will not be released to any other person, including other members of the project team. Identifiable information will never be used in a publication or presentation. All interview responses will be transcribed without identifiable information (i.e. only identified with a passkey). Interviews will be audio-recorded and de-identified during transcription for analysis. De-identified data will be stored according to NUS/GIS Research Data Management Policy to ensure confidentiality and protect the privacy of participants. Only the research team will have access to the data, which will be analyzed using thematic and content analysis techniques to identify common themes. Research data used in publications will be kept for a minimum of 10 years before being discarded. The coded data will not be used for future research, nor will participants be contacted for future studies.

What are the possible discomforts and risks for participants?

We do not anticipate any discomfort or risks as the focus of the interviews is on validating the patient information sheet and informed consent document. If at all during the interview you do experience distress, you are welcome to withdraw your participation in the study. Your participation is voluntary and you are welcome to stop at anytime. Your clinical care will not be influenced by your decision to participate. If you do experience discomfort or stress, you are welcome to meet with Mrs Tan Yee Pin, psychology oncologist, at the National Cancer Centre Singapore. She can be contacted at 6436.8000 or nsstyp@nccs.com.sg. Alternatively, researchers on this study can facilitate the introduction. This to ensure that any possible discomfort be addressed to your satisfaction.

Will there be reimbursement for participation?

For the interview, you will receive a $50 NTUC voucher.

What are the possible benefits to me and to others?

There is no direct benefit to you by participating in this research. You will, however, contribute to developing the informed consent process for tumour testing in Singapore.

Can I refuse to participate in this research?

Yes, you can. Your decision to participate in this research is voluntary and completely up to you. You can also withdraw from the research at any time without giving any reasons, by informing the principal investigator and any data collected will be discarded. Your clinical care will not be influenced by your participation.

Whom should I call if I have any questions or problems?

Please contact Jyothi Thrivikraman at **+65 68088207** and **thrivijk@gis.a-star.edu.sg** for all research-related matters and in the event of research-related injuries. This study has been reviewed by the SingHealth Centralised Institutional Review Board for ethics approval. If you have questions about your rights as a participant, you can call the SingHealth Centralised Institutional Review Board at 6323 7515 during office hours (8:30 am to 5:30pm). If you have any complaints about this research study, you may contact the Principal Investigator or the SingHealth Centralised Institutional Review Board.

Consent Form

Project Title: *Developing the Informed Consent Procedures for Molecular Profiling in Singapore*

Principal Investigator:

Dr. Patrick Tan
Senior Group Leader, Genome Institute of Singapore
Principal Investigator (Adjunct),National Cancer Centre, Singapore
Phone: +65 68088053

Email: chuah2@gis.a-star.edu.sg

I hereby acknowledge that:

1. I have read the participant information sheet that explains the procedures in this research study. I understand its contents.
2. I have had the opportunity to ask questions and am satisfied with the explanation and answers to my questions.
3. I also understand that I do not need to participate in this interview and can decline at any time.
4. I agree to the audio-recording of my interview.
5. I can withdraw from the research at any point of time by informing the Principal Investigator and all my data will be discarded.
6. I understand that researchers will attempt to contact me up to three times using my preferred method of communication to schedule interviews.

Consent Declaration

Consent to Interviews	
☐ agree	☐ do not agree
Interview Scheduling	
☐ Immediately (on the same day as consent is granted)	☐ At a later day and time to be contacted by contact me via phone/email (*circle preferred method*). Phone: _____ Email:_____

Participant's Name: _____

Participant's Signature: _____

Date: _____

Email: _____ Telephone Number: _____

Statement by the person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the study procedures and process. I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this information sheet and consent has been provided to the participant.

Print Name of person taking the consent_____

Signature of person taking the consent_____

Date _____

APPENDIX SIX: CLINICIAN INTERVIEW GUIDE

Thank you for your participating in this interview. Your participation is invaluable and will help us develop the informed consent process for the POLARIS Cancer Panel test. My name is Jyothi Thrivikraman and I will be conducting this interview. As discussed over email, the POLARIS Cancel Panel Test is part of a larger project at the Genome Institute of Singapore (GIS). POLARIS is an A*Star funded initiative developing personalised medicine to improve diagnosis, treatment and health care outcomes in Singapore.

For this interview, I would like to ask that you focus your responses on the informed consent process for this test and not on other clinical tests currently being utilized by your clinic. Your identity will remain confidential, so please feel free to be honest in your opinions. Do you have any questions for me?

Have you reviewed the informed consent document emailed earlier? Do you have any questions on that? (*Get consent after reviewing document*)

Questions:

In order to implement this test, we need to consider the consent form content as well as how it will integrated into practice. I will give you more information about the test shortly, however, before we begin the questions, could you please speak about your position at the National Cancer Centre and in what capacity you see or are involved with cancer patients.

1. **Cancer Diagnosis and Genetics**
    a. I am trying to understand a bit better about how patients receive and understand their cancer diagnosis. Could you speak about this from your experience?
    b. Does anything come to mind when you hear the words "genetic or genomic" (Simon, Williams et al. 2011)
    c. Do you discuss with your patients how genetic mutations may play a role in cancer development?
        i. Can you explain the difference between germline and somatic mutations?

2. **Delivery of Study Details:**

Provide a short review of germline vs. somatic---repeating what was said or correcting the stakeholder. Now, let me take a few moments to review details about the test. *The POLARIS cancer panel test is available to colon and GIST cancer patients to tailor treatment "known as precision/ personalised medicine". Are you familiar with this term? If not, this involves sequencing multiple genes known to be involved in tumour development to generate a molecular profile. Treatment most effective according to the tumour molecular profile would then be administered, i.e. "targeting therapy". A clinical report will be issued on the mutation analysis of 5 genes so that treatment can be tailored according to the profile of the tumour. The patient is charged for this test as it is in addition to their standard treatment. There is also the option to have an additional 85 genes analysed and these findings will be reported under research/discovery genes. This is because the implications of these genes for treatment are not yet fully understood so they fall under "research" rather than clinically "actionable". As we go through our questions on the informed consent process, please keep in mind these points (review the key points). Now let me go through the clinical journey for a typical patient. A patient comes to the National Cancer Centre and is diagnosed with colon or GIST cancer requiring chemotherapy. The patient is offered the POLARIS cancer panel test; both the clinical and research components are presented and patients have the option of being involved in the research component. If*

the patient declines the research portion, only the clinical molecular profiling of 5 genes is reported to their treating clinician. If the patient agrees to the research component, an additional 85 genes are analysed and reported to their treating clinician. There is another component to the consent process involving the storage of the tumour molecular data. The data is stored in the POLARIS Singapore Cancer database and data may be obtained in a de-identified manner by Singaporean and international researchers for additional studies or identifiable under IRB approval. I hope my explanation is clear. Please let me know if you have any questions.

a. Now that you understand the POLARIS cancer test a bit better, can you tell me how you envision this test being incorporated into clinical practice? (*probe about other similar tests…i.e. the foundational medicine test*)
    i. Who should deliver the information about the clinical and research components of the POLARIS test? (*Probe about clinician, nurse, study coordinator, combination of individuals*)
        1. To clinician: Would you feel comfortable answering questions about the research components of this study to your patients and seeking their consent?
    ii. Do you feel that you know enough about somatic mutations in your patients' cancers to adequately explain this test? (*Probe on ways that education on genomics and cancer can be improved*)
b. Based on your experiences and understanding the POLARIS cancer panel test, how will patients feel about the research component of the test? What sort of information would they need in the informed consent documents? (*probe about public good/data may help them in the future*)
c. The knowledge around cancer and genetics is evolving rapidly. How should the communication around new clinical trails and findings be shared between clinician and POLARIS to ensure that the cancer panel is most current? (*probe on POLARIS liaising with clinician or clinician liaising – trying to determine the best way for POLARIS to stay up to date on latest research*)

3. **Model of Informed Consent for Research:** There will be no consent form for the clinical portion of the test. The informed consent process should cover the return of the 85 discovery genes, the storage and sharing of tumour genetic data and return of new research findings. I want to understand your thoughts on the type of patient informed consent that you think would be ideal for the research part of the test. There are many types of consent: implied consent, open/traditional consent, tiered/staged consent, blanket consent, categorical consent, or specific consent. Are you familiar with these different types? *(If not familiar provide a quick summary of them*)
    a. For the POLARIS cancer panel test, which type of informed consent model would be best suited for the test?
        i. *Probe on why*
    b. What concerns would you have on data security, governance structure and future research protocols would be critical to patients, health care providers, IRB members for each of the components that need to be covered in the informed consent document? (Caulfield, McGruire et al. 2008). How should they be discussed in the informed consent document?

    Storing and Sharing of Data: Now I would like to discuss how the informed consent documents should frame the storing and sharing of tumour genetic data.
        i. What are your thoughts on how this should be framed in the informed consent documents?
        ii. From your experience, do you envision patients having concerns with storing of their tumour genetic data for an unidentified time frame? Sharing of their de-identified data both locally and globally?
        iii. Can you discuss the role of patient empowerment in clinical and research decisions for sharing of molecular data. (*probe on altruism and public good concepts)*
    c. For IRB members:

i. What information (if any) does the IRB require in consent documents with respect to genetic or genomic studies? (Simon, Williams et al. 2011))
ii. What details would IRB require for sharing and storing of molecular data?
    1. Would researchers need Singhealth IRB review to access data if in de-identified form?
    2. How are decisions made to support re-linking of data in case of research findings?

Return of Findings: Now I would like to discuss the return of findings. As indicated earlier, all the results will be returned to the clinician. There are two sets of findings. The first would be in the discovery sheet immediately upon completion of the test and future new findings.

Discovery Sheet

- Do you think you will return the discovery sheet findings to the patient?
- How comfortable are you to speak about the results from the discovery sheet?
    - While this is a somatic test, some of the genes on this panel could have germline implications (i.e. BRCA). What would you do if a somatic BRCA mutation were found? Would you (and how) relay this information back to the patient?
- The current plan is for the discovery sheet results to be returned to the ordering clinician. Do you think this is the best plan? What alternative strategies could you propose? Discuss infrastructure and cost implications
    - *probe on staff needed and cost to return discovery sheet results*
    - *Educational requirements to stay up to date on latest genomics research regarding treatment*

Future Findings from Research

- Are there any critical findings to be returned to the patient? (*probe on the idea of actionability, prevention*)? Can you discuss your ability to return findings and provide guidance / support to patients?
    - Who should return the findings? (*this is a somatic test, but could patients need psychosocial support?*)
    - What should be done with information gathered from tumour genetic testing if patients do not want to know the results?
- Length of time for return of new research findings
- Discuss infrastructure and cost implications
    - *probe on staff needed and cost to return discovery sheet results*
    - *Educational requirements to stay up to date on latest genomics research*

Withdrawal: As molecular profiling data will be stored and shared with researchers, withdrawal will become complicated.

i. Infrastructure implications (how will withdrawal be managed?)
ii. Do you support a timeframe by which research study participants are allowed to withdraw? (*probe on who the patient should liaise with: health care provider, study team member etc.*)

While the clinical implementation of the POLARIS cancer panel test focuses on somatic testing, I would like to discuss your thoughts on informed consent if the test were to include germline data collection via blood to compare mutations in the tumour tissue. How would you manage germline incidental findings (i.e. BRCA)? How do you ideas about the type of informed consent, return of new findings and infrastructure requirements change with the incorporation of germline testing?

For health care providers:

i. In the event of germline implications, how would your ability to provide patient support alter---are there any things that would need to be done differently between somatic vs. germline implications when returning findings? (probe regarding counseling, communication to family members...)
ii. What should be done with information gathered from germline testing if patients do not want to know the results?

For IRB members:

iii. As indicated above, the current cancer panel test only focuses on somatic data via molecular profiling of tumour tissue. In the hypothetical situation that germline testing would be incorporated into the test, how would IRB requirements for consent, re-linking of data and return of findings change?

Withdrawal

iii. Would parameters for withdrawal change if the data included germline profiling along with access to medical records?

Just to reiterate: the current POLARIS Cancer Panel Test does not include germline testing. The last set of questions were hypothetical to inform future iterations of the informed consent procedures.

These conclude our formal questions. Do you have any additional comments or questions for me?

Lastly, could you please provide me with details of other key stakeholders that would need to be interviewed in developing the informed consent process for the POLARIS cancer panel test?

Thank you for your time.

Types of consent (Adapted from (Appelbaum, Fyer et al. 2014)

- Implied: Consent is not explicitly sought from participants to use their samples in research
- Open/Traditional: Consent is sought from participants either at or prior to sample collection in any and all future research without the need to obtain any further consent.
- Tiered/Staged Consent: Consent is obtained in stages for different parts of a study; this gives participants multiple options.
- Blanket: Similar to open/traditional consent, but the participants delegate their decision making authority to an IRB or another institution for specific research projects.
- Categorical: Consent for data to be used for specific categories of research, but allows researchers to re-contact participants to use samples in research outside of the specified categories.
- Specific: Consent for data can be used for specific categories of research, but may have provisions for researchers to re-contact participants to use samples in research outside of the specified categories.

REFERENCES:

Appelbaum, P. S., et al. (2014) Reserachers' views on informed consent for return of secondary results in genomic research. Genetics in Medicine

Caulfield, T., et al. (2008). "Research Ethics Recommendations for Whole-Genome Research: Consensus Statement." PLoS Biology **6**(3).

Simon, C. M., et al. (2011). "Informed Consent and Genomic Incidental Findings: IRB Chair Perspectives." Journal fo Empirical Research on Human Research Ethics.

APPENDIX SEVEN: PATIENT INTERVIEW GUIDE: DEVELOPING THE INFORMED CONSENT PROCEDURES FOR MOLECULAR PROFILING IN SINGAPORE

Introduction

Thank you for participating in this interview. Your participation is invaluable and will help us develop the informed consent process for the POLARIS Cancer Panel test. My name is Jyothi Thrivikraman and I will be conducting the interview today.

We are interested in hearing your point of view; you won't hurt my feelings or make me feel good with whatever opinions you might give.

We are seeking your opinions on the informed consent document in front of you. This document lays out the process and procedures for the POLARIS cancer panel test. The POLARIS Cancel Panel Test is part of a larger project at the Genome Institute of Singapore (GIS). POLARIS is an A*Star funded initiative developing personalised medicine to improve diagnosis, treatment and health care outcomes in Singapore. Personalised medicine means treatment tailored for your specific health condition and genetic profile. The POLARIS cancer panel test will be able to identify genetic mutations for certain cancers to improve your treatment, but also analyse additional genes from your tumour for research. Before the test is offered at the National Cancer Centre, researchers need to ensure that you as the patient understand the purpose of the test and how the genetic data will be used.

Before we start taking about the specifics of the informed consent document in front of you, I would like to ask you a few questions on your understanding of genetics, cancer and informed consent.

Awareness around genetics, cancer and informed consent

a. Please tell me your thoughts on what are genes or genetics? How do you think cancer develops?
b. Have you ever heard of genetic testing for cancer? What did you hear and where?
    i. When you think about cancer, genes or mutations are there certain words or ideas that come into your mind?
    ii. Probe more on ideas of a "damaged" gene
c. What are your thoughts / beliefs on genetic testing?
    i. What happens if you were ill and had the option of getting a genetic test to understand how your disease developed? Would you want this disease specific genetic test to personalize your treatment? Why or why not?
    Probe: What are your thoughts on genetics and inherited diseases? Focus on cultural, religious beliefs and/or views of family members. Who do you think controls illness
d. What is your understanding of informed consent?

Probe: How much information do you want on a study? And who should be involved in your decision to participant; would you need to consult with anyone specifically. Would you participate because your doctor or nurse asked you to? Would you want to speak with a genetic counselor about testing? I will

now give you a few minutes to review the draft of the informed consent document that is in front of you.

Questions on the IC document. I will now ask you some questions to make sure you are clear on this informed consent document. There are no right or wrong answers. We are just trying to understand how best to develop this document so that it is clear.

1. What is the purpose of this research project?
    a. Do you understand the differences between the two parts of the POLARIS test? What is involved in this research project?
2. What will happen to your genetic data?
    a. Discuss about ways to keep data privacy?
    b. What are the possible risks?
    c. What are the possible benefits?
3. How do you feel about the idea of your genetic data being stored indefinitely?

    Is this information on data storage and security sufficient and clear? *Probe: How do you feel about it being stored in Singapore? How do you feel about it being stored outside of Singapore and accessed by researchers in other countries?*

4. Will I find out about the results of the research?
    a. Difference between discovery sheet and future findings needs to be discussed.
5. What are your options if you have any questions on the research project?
6. What happens if you change your mind about sharing and storing of my genetic data?

Additional Questions:

1. Would you want to participate in research project like this?
    a. Why or why not?
    b. What sort of additional information would you want to know
    c. If no, what kinds of information would make you change your mind about the research participation?
2. If researchers discovered something serious about your heath, do you think they should let you know? (Beskow, Friedman et al. 2010)

Thank you for time. Do any of you have any final comments or questions before we conclude the session?

References

1. Beskow, L. M., et al. (2010). "Developing a simplified consent form for biobanking." PLoS One **5**(10): e13302.
2. Caulfield, T., et al. (2008). "Research Ethics Recommendations for Whole-Genome Research: Consensus Statement." PLoS Biology **6**(3).

APPENDIX EIGHT: PATIENT INFORMATION SHEET AND CONSENT DOCUMENT SHARED WITH PATIENTS

Title: Polaris Tumour Profile Test

What is the purpose of this research?

You have been diagnosed with cancer and have agreed to the POLARIS tumour profile test. This test involves accessing your tumour tissue from the Singhealth tissue biobank, which was collected at the time of your biopsy. The results of this test will be used to guide the best treatment for your cancer.

This information sheet invites you to participate in an *optional* research component of the POLARIS tumour profile test. Your decision to participant or not will have *no* impact on your cancer treatment. The research component of the POLARIS tumour profile test will look at additional genes in your tumour. Participation does not involve additional surgery or tests.

POLARIS is interested in learning how genetic variations in cancer can help guide treatment. Some gene variants are already used in clinical care. Researchers are still learning about how additional gene variants could impact clinical care. The information learned from this research could help to treat cancer patients better in the future. Your genetic data will also be stored and shared with researchers outside of POLARIS, both within Singapore and overseas.

POLARIS is an initiative developing personalised medicine to improve diagnosis, treatment and health care outcomes in Singapore. Personalised medicine means treatment tailored for your specific health condition and genetic profile. The POLARIS tumour profile test (both clinical and research components) is performed in an internationally certified laboratory (CAPS) and will be able to identify genetic variations for certain cancers to improve your treatment, but can also analyse additional genes from your tumour for research.

You may have some questions on what is meant by. Your doctor will give you a brochure that explains all this information. Please take a few minutes to review the brochure. If you have any questions please ask your doctor. You are also welcome to schedule time with the POLARIS clinical coordinator at Singhealth to discuss genetics, cancer, research genes, and the sharing of your genetic data. Please let your doctor know if you wish to speak the POLARIS research coordinator.

You have given a brochure that explains the research test. Please take a few minutes to review the brochure. And if you have any questions. If you wish to speak to Polaris research coordinator contact the research coordinator directly.

Who can participate in the research?

If your doctor thinks you can benefit from the clinical part of the POLARIS test, you will become eligible for the research part. You are *not* obligated to participate in the research. Your decision to participant will *not* influence the clinical part as this is separate from the research component. Also, your decision will *not* impact on the care and treatment you receive for your cancer. Any one who has done the Polaris tumour is eligible for the discovery profile.

What will be done after I take part in this research?

Here is what will happen:

1. If you consent to the research component, additional genes will be analysed and stored in the POLARIS database with your identifying information such as your name, NRIC/passport number, home address, telephone number and date of birth. Only your tumour profile will be stored, and not your tissue.
2. Other researchers in Singapore and overseas may access your tumour profile data for additional studies but ONLY after the data have been de-identified. That is, any information that identifies you (see point 4 above) with your tumour profile data will be removed. This is in line with the Singapore's Human Biomedical Research Act (2015). Stored both identified for sharing with physicians and researchers with IRB approval in Singapore..in ccordance with the HBR 2015 and PDPA and de-identified for sharing researches

Will I find out the results of the research?

You can opt to receive the results of the research component; however, additional research findings may not be known for many years as researchers compile tumour profile data from many individuals. The genes that are analysed from the research component have not been linked to any clinically proven treatment for your cancer. The return of these research results would not be used to determine your treatment. You are welcome to discuss the results of the research component with the POLARIS clinical coordinator.

Will I be paid to participate?

No.

Are there any benefits to participating in the project?

For the research component, you will not receive any direct benefits from submitting your tumour profile data to POLARIS for future research.

The main reason you may want to take part is to help researchers generate knowledge that may benefit patients in the future. Your tumour profile data will be available for any research after ethics approval as per the Singapore Human Biomedical Act (2015). While it difficult to know exactly what research will be done with your data, over the next decade researchers will generally be aiming to:

- analyse the genetic information using a process called 'sequencing'; and
- study genetic variation.

What are the risks or discomforts of participating?

There are no physical risks or discomfort as no additional procedures or consultations are required. The main risk is that someone could access you discovery profile data without authorisation. If this data were perceived (misinterpretation) suggested something serious about your health, it could be misused. While the chance of this happening is extremely low, we cannot guarantee this could never happen. However, your privacy and the confidentiality of your data are very important to us and we will make every effort to protect them. Perceived as having suggestion something

How will your tumour profile data stored?

The POLARIS team will store your personal information (name, NRIC/passport number, home address, telephone number and date of birth) and, when needed, will require access to your hospital medical records to retrieve relevant clinical information. This information will only be accessed by authorized POLARIS personnel and with permission from the hospital. Your data will be stored in highly secure online databases (i.e. a server/cloud provider) that meet international security and safety standards.

What procedures are in place to protect your privacy?

In accordance with the Singapore Human Biomedical Research Act (2015), only de-identified data will be shared with researchers outside of POLARIS, either in Singapore or overseas. Identifiable information will never be used in a publication or presentation, nor will it be shared with anyone outside of POLARIS. Only authorized personnel in POLARIS will have access to your identifiable information.

Your de-identified data may be shared with researcher overseas and may be moved and stored in different countries. In order to keep your information confidential, numerous protections are in place. Specifically:

- Your personal details and relevant clinical information will be kept separate;
- Your data will be encrypted and coded to reduce the chance of re-identification. Encryption keys will be held off-site by a third party as required by law; and
- Stringent security measures will reduce the likelihood of unauthorised access or misuse. All researchers will have to respect the laws and ethical guidelines that apply to biomedical research in Singapore.

Can I change my mind after I decide to participate?

Yes. You can change your mind about participation in the research component of the test at anytime. However, once your tumour profile data has been sent to other researchers, we are unable to retrieve that data from them because the data will have been de-identified. If you choose to withdraw, the data stored in the POLARIS database will be deleted. You can contact the POLARIS clinical coordinator to withdraw from any future release of data.

Who can I contact if I have questions or concerns?

If you have any questions at anytime, please contact the POLARIS clinical coordinator. Your questions should be answered to your satisfaction before you sign the consent form.

Patient Consent Form

Title: *POLARIS Tumour Profile Test*

I hereby acknowledge that:

1. I have read the participant information sheet that explains my role in this research.
2. I understand that I am granting POLARIS permission to access my tumour tissue from the Singhealth tissue bank for tumour profiling for the research component.
3. I understand that no additional tests or procedures will need to be done as a biopsy has been completed.
4. I have had the opportunity to ask questions and am satisfied with the explanation and answers to my questions.
5. I understand that I can decide if I want to receive the results of the research component of the tumour profile.
6. I understand that I can decide if I wish to be recontacted to receive information from future research findings pertaining to my health.
7. I understand that my genetic data will be stored in identifiable format by POLARIS for a period of 10 years.
8. I understand that my de-identified genetic data will be shared with researchers in Singapore and overseas.
9. I understand I can withdraw from the research at any point of time by informing the POLARIS clinical coordinator. I understand that genetic data already shared with researchers outside of POLARIS cannot be withdrawn.

Consent Declaration *(Circle the Appropriate Consent Declaration)*

I consent for storing my identifiable data with POLARIS	Yes	No
I consent for POLARIS to share my de-identified data with other (authorized) researchers	Yes	No
I consent that I would like to receive the results of the research component	Yes	No
If within the next 10 years, researchers make clinically relevant findings I consent that the POLARIS clinical coordinator can recontact my treating physician and myself for any relevant future findings. Recontact in the future for additional research/clinical trials future research	Yes	No

_____	_____	_____
Signature of patient	Name of patient	Date
_____	_____	_____
Signature of witness	Signature of Witness	Date
_____	_____	_____
Signature of Translator (if relevant)	Name of Translator (if relevant)	Date

APPENDIX NINE: DEMOGRAPHIC CHARACTERISTICS OF PATIENTS INTERVIEWED

Number	Cancer Diagnosis	Gender	Age	Ethnicity	Transcribed
1	Breast	Female	39	Chinese	Transcribed
2	Breast	Female	46	Chinese	Transcribed
3	Breast	Female	52	Chinese	Transcribed
4	Breast	Female	55	Chinese	Transcribed
5	Breast	Female	59	Chinese	Transcribed
6	Breast	Female	60	Chinese	Transcribed
7	Breast	Female	60	Chinese	Transcribed
8	Colon	Male	62	Chinese	Transcribed
9	Breast	Female	40	Indian	Transcribed
10	Breast	Female	53	Indian	Transcribed
11	Breast	Female	69	Indian	Transcribed
12	Breast	Female	59	Bangladeshi	Not Transcribed
13	Breast	Female	43	Bangladeshi	Not Transcribed
14	Breast	Female	49	Chinese	Not Transcribed
15	Breast	Female	54	Chinese	Not Transcribed
16	Breast	Female	52	Chinese	Not Transcribed
17	Breast	Female	40	Indian	Not Transcribed
18	Breast	Female	58	Indian	Not Transcribed
19	Breast	Female	64	Indian	Not Transcribed
20	Breast	Female	35	Malay	Not Transcribed
21	Breast	Female	63	Malay	Not Transcribed
22	Breast	Female	68	Malay	Not Transcribed
23	Breast	Female	27	Malay-Chinese	Not Transcribed
24	Breast	Female	50	Pakistani	Not Transcribed
25	Breast	Female	58	Philipino	Not Transcribed
26	Breast	Female	46	Vietnamese	Not Transcribed

APPENDIX TEN: GLOSSARY OF TERMS

Types of Consent	
Implied consent	Whereby consent is not explicitly sought from participants to use their samples in research.
Blanket consent	Consent that is sought from the participant once, either at or prior to sample collection, for use in any and all future research without the need obtain any further consent.
Broad consent	Consent that is sought from the participant once, either at or prior to sample collection, for use in any and all research without the need obtain further consent from the participant, who then delegates their decision making authority to an IRB (or another institution) for specific research projects.
Categorical consent	Consent that is sought from the participant to use samples in particular categories of research, and may include an option that allows researchers to recontact participants for consent to use samples outside of nominated areas of research.
Specific consent	Consent that is sought from the participant to use samples in specific research projects only, and may include an option that allows researchers to recontact participants for consent to use samples in other projects.
Tiered consent	Provision of multiple options for participants to chose the type of consent they wish to provide.
Types of Consent Methods	
Opt out	Whereby consent is not explicitly sought for a given action, but participants are informed about the option to withdraw.
Opt in	Whereby verbal or written consent is explicitly sought from the participant to use samples in research.
Types of Withdrawal Options	
Tiered withdrawal	Whereby participants are given numerous options to withdraw in varying degrees. I.e. to withdraw from further contact while leaving samples and data in the study, or withdraw samples while leaving data, or withdraw all samples, personal information and discontinued use of data
Single withdrawal	Whereby participants are given the option to either continue participation or withdraw completely.

APPENDIX ELEVEN: DRAFT BROCHURE FOR PATIENTS

PLACE STAMP HERE

What is informed consent and why is it needed?

- Informed consent protects your rights by making sure you understand your rights as a participant in a study.
- Informed consent gives you a clear understanding of the purpose, benefits and risks involved[1].
- It is also the time for you to ask any questions about participating in the research.

Would participating (or not) affect my treatment?

- Participating (or not) will not affect your current treatment. They are independent of each other.

Bibliography

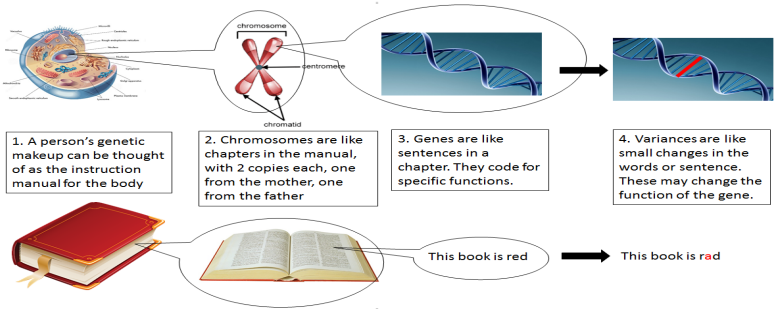
1. *Genomics And World Health*. Geneva: World Health Organization, 2002.
2. Singapore Statutes Online. *Human Biomedical Research Bill*. Singapore Statutes Online, 2015

Contact Us

Insert Details Here

Informed Consent for the POLARIS Discovery Profile

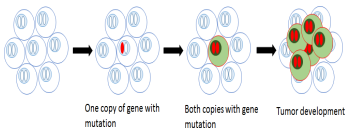
1. What are DNA and genes?



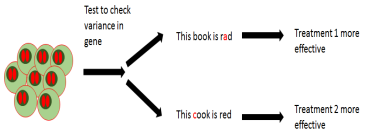
4. What is the difference between clinical and research gene findings?

Normal Genes	This book is red →	No impact on treatment
Clinical Genes	This cook is red →	Treatment 1 effective
	This book is rad →	Treatment 2 effective
Research Genes	This boon is red →	No data on treatment effectiveness → Future research → Treatment X effective

2. How do variants cause cancer?

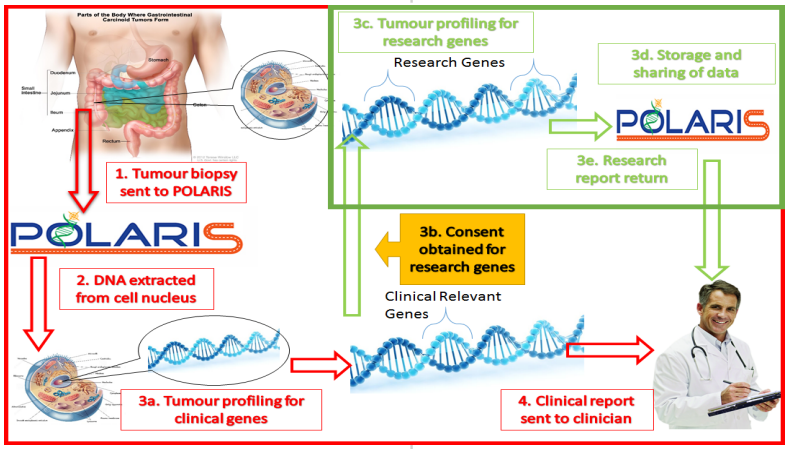


3. What is Tumour Profiling?



1. Tumour Profiling identifies the variants in a gene.
2. Tumour treatments respond differently to genetic variants.
3. Tumour profiling allows more effective treatment to be selected

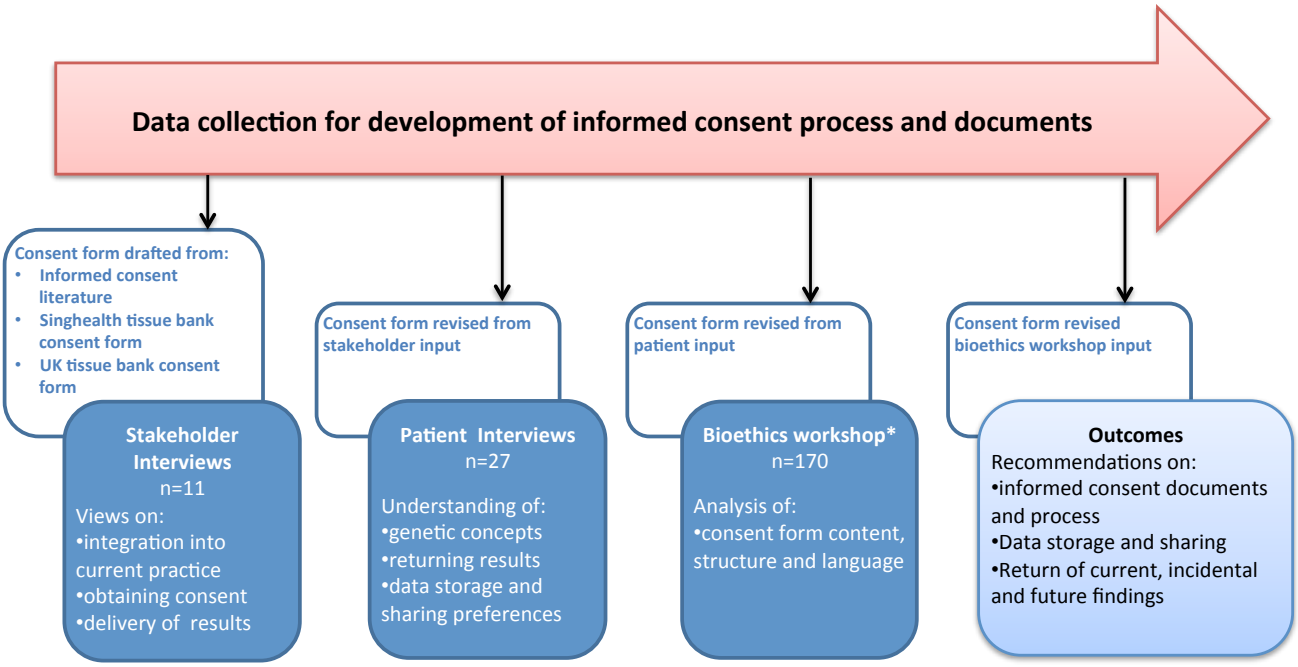
5. POLARIS™ Tumour Profile Test Process



Clinical tumor profile in red box

Informed Consent for research genes in green box

APPENDIX TWELVE: CONSENT DEVELOPMENT PROCESS



*Advancing Research Ethics in Singapore, Ethical and Legal Challenges in a New Regime, Singapore, Nov 2015

APPENDIX THIRTEEN: INFORMED CONSENT DOCUMENT

INFORMATION SHEET

You are invited to take part in a research project called the **POLARIS Discovery Profile**.

POLARIS is part of A*STAR's Genome Institute of Singapore. Established in 2013, POLARIS is focused on the application of clinical genomics in the diagnosis and treatment of diseases in Singapore and the region. In partnership with hospitals and local researchers, POLARIS has launched tests to provide clinically actionable information to patients and doctors; these tests are within the scope of personalized medicine, which is treatment tailored to individual's specific health condition and genomic profile.

Before you decide to take part in this research, please read through this information sheet carefully and refer to the brochure that explains tumour profiling and the POLARIS Discovery Profile research test. You may discuss this information with others if you wish. If anything is not clear, or you would like more information, please speak with our dedicated research coordinator whose contact details are below. More information about POLARIS is available at https://www.a-star.edu.sg/polaris/

Contact Details

[Enter Contact Details for POLARIS Research Coordinator]

What is the purpose of the POLARIS Discovery Profile?

Currently, POLARIS offers a clinical test to identify mutations in five genes associated with tumour development to determine the best possible treatment for your cancer. This test is known as the POLARIS Tumour Profile.

The purpose of the POLARIS Discovery Profile is to research mutations in additional genes of the same tumour. The genetic information generated will be stored and shared with other researchers to learn how they also contribute to the growth of cancer and if they could be used to inform clinical care in the future.

Why have I been invited to take part in the POLARIS Discovery Profile?

Your oncologist has ordered a test from POLARIS to determine whether your tumour has mutations in any of the five genes currently used in clinical care. Anyone receiving this test may also take part in the Discovery Profile provided that they are legally able to consent to research (i.e. are mentally competent and over 21 years of age).

What will be done if I take part in the POLARIS Discovery Profile?

If you consent to this research, the Discovery Profile will analyse the same tumour sample for the additional gene mutations. Results of the Discovery Profile will be stored on the POLARIS database along with your NRIC number and date of birth. No additional consultations, procedures or tests are required.

Researchers in Singapore and overseas may apply to access information or data that is stored with POLARIS. This information will NOT be supplied with your IC or date of birth; that is, your Discovery Profile data will be *de-identified*. The de-identified data will ONLY be shared with other researchers in accordance with the Singapore Human Biomedical Research Act (2015) and the Personal Data Protection Act (2012).

Do I have to take part in the POLARIS Discovery Profile?

No. It is entirely up to you to decide whether or not you take part in the Discovery Profile. If you do decide to take part, you will be asked to sign a consent form.

Why do you need my written informed consent?

Your participation in the Discovery Profile is entirely voluntary. By signing the consent form, you would be confirming your understanding of the Discovery Profile and your willingness to take part. This is also your opportunity to ask any questions about what participation entails.

In particular, you would be agreeing to:

- Allow POLARIS to analyse your tumour for the additional gene mutations and store this data with POLARIS along with your IC and date of birth.
- Allow de-identified data generated by the Discovery Profile to be shared with researchers both in Singapore and overseas.

Even if you do consent to participate, you would be free to withdraw at any time if you wished to do so (see below). Please ask the POLARIS research coordinator if you have any concerns with what taking part might involve.

Will I find out the results of the POLARIS Discovery Profile?

You can opt to receive the results of the Discovery Profile. However, the genes analysed on the Discovery Profile are only for research; there are no treatments available for your cancer based on the results of your Discovery Profile. The results would *NOT* be used to determine your cancer treatment and would *NOT* be of any clinical value. The Discovery Profile is solely for the purposes of research. Once the results are available, the POLARIS research coordinator will call or email to schedule time to review the results with you. If you wish to review your results, you will need to provide your contact details so POLARIS can get in touch with you. These contact details will only be used by the POLARIS research coordinator to review your results and will not be shared. These Discovery Profile results will also be shared with your oncologist and placed in your medical records if you opt to receive the Discovery Profile results.

Are there any benefits to taking part in the POLARIS Discovery Profile?

You will not receive any financial gains or benefits from taking part in the Discovery Profile; irrespective of whether the use of data might ultimately lead to profit. The main reason you may want to take part is to help researchers generate knowledge that may benefit patients in the future.

What are the risks of taking part in the POLARIS Discovery Profile?

Taking part in Discovery Profile should not cause you any harm. There are no physical risks or discomforts as no additional procedures or consultations are required. Participation involves minimal risks in relation to the use of personal information. However, great care will be taken to ensure the confidentiality of all data as outlined in the next section and the risk to participants of a breach of confidentiality is considered very low.

How will my Discovery Profile data be stored?

POLARIS will store your Discovery Profile data along with your NRIC and date of birth in highly secure online databases (i.e. a server/cloud provider) that meet international security and safety standards. Your Discovery Profile data will be stored separately from your NRIC and data of birth; only authorized POLARIS personnel would be able to link the information. POLARIS may require access to your hospital medical records to retrieve relevant clinical information. This information will only be accessed by authorized POLARIS personnel and with permission from the hospital's Institutional Review Board (IRB).

How will my privacy be protected?

POLARIS has put a number of rigorous procedures in place to protect the privacy of participants and keep your information confidential. Specifically:

- Your Discovery Profile data and identifiable data will be stored in separate computers from clinically relevant information.
- Computer security to block unauthorized access (for example, by "hackers") to the computers that hold personal information.
- Your data will be encrypted and coded to reduce the chance of re-identification. Encryption keys will be held off-site by a third party as required by law
- Access to your information is restricted within POLARIS, and all staff sign confidentiality agreements as part of their employment contracts.
- Data or samples provided to researchers will be de-identified and will not include personal identifying information.

These security measures should prevent identifiable information from being used – inadvertently or deliberately – for any purpose other than to support the project. All researchers who are given access to your Discovery Profile results are required to abide by the laws and ethical guidelines that apply to biomedical research in Singapore.

Who can access my Discovery Profile data?

Discovery Profile data will be available only to researchers who have relevant scientific expertise and ethics approval for their planned research. In accordance with the Singapore Human Biomedical Research Act (2015), only de-identified data will be shared with researchers outside of POLARIS, either in Singapore or overseas. Identifiable information will never be used in a publication or presentation, nor will it be shared with anyone outside of POLARIS. Only authorized personnel in POLARIS will have access to your identifiable information.

Your de-identified Discovery Profile data may be shared with other researchers in Singapore and overseas and may be moved and stored in different countries. This could include researchers who are working in public research institutions or in commercial companies looking for new treatments. Data shared with researchers will be available for free. POLARIS also encourages publication of research results to ensure that knowledge of new findings is widely disseminated.

While it is impossible to anticipate all future research uses, your Discovery Profile results will only be released for research that is consistent with POLARIS's stated purpose of developing clinical applications for the treatment of disease.

Insurance companies and employers will not be given any individual's information, or Discovery Profile results, and nor will we allow access to the police, security services, relatives or lawyers, unless forced to do so by the courts in Singapore.

How do I withdraw if I want to do so?

POLARIS Discovery Profile will be most valuable if few people withdraw, so potential participants are asked to discuss any concerns that they might have with the POLARIS research coordinator before agreeing to take part.

You can withdraw from the POLARIS Discovery Profile research at any time. However, once your Discovery Profile has been sent to other researchers we will be unable to retrieve that data because it will have been de-identified. Only the data stored in the POLARIS database will be deleted along with any identifying information.

To withdraw, please contact the POLARIS research coordinator at [insert phone] (Mon-Fri; 9.00am to 6.00pm) to discuss your options. If, having discussed the options and your concerns, you decide to withdraw then we will send you a Withdrawal Form to confirm your wishes in writing.

Consent Form: POLARIS Discovery Profile

I hereby acknowledge that:

1. I have read the information sheet that explains my role in this research.
2. I understand that I am granting POLARIS permission to analyse my tumour tissue for the Discovery Profile.
3. I understand that I am granting POLARIS permission to access my hospital medical records if needed.
4. I understand that I will not receive any financial benefits from the use of the Discovery Profile data.
5. I have had the opportunity to ask questions and am satisfied with the explanation and answers to my questions.
6. I understand that I can decide if I want to receive the results of the Discovery Profile and will need to provide my contact details to the POLARIS Research Coordinator.
7. I understand that my Discovery Profile results will be sent to my treating oncologist and placed in my medical file if I select to receive the results.
8. I understand that POLARIS will store the Discovery Profile data along with my identifiable information for a period of 10 years.
9. I understand that my de-identified Discovery Profile data will be shared with researchers in Singapore and overseas.
10. I understand I can withdraw at any point of time by informing the POLARIS research coordinator. I understand that genetic data already shared with researchers outside of POLARIS cannot be retrieved.

Consent Declaration *(Circle the Appropriate Consent Declaration)*

I consent to participate in the POLARIS Discovery Profile	Yes	No
I consent to have the POLARIS research coordinator contact me to discuss the Discovery Profile results	Yes	No

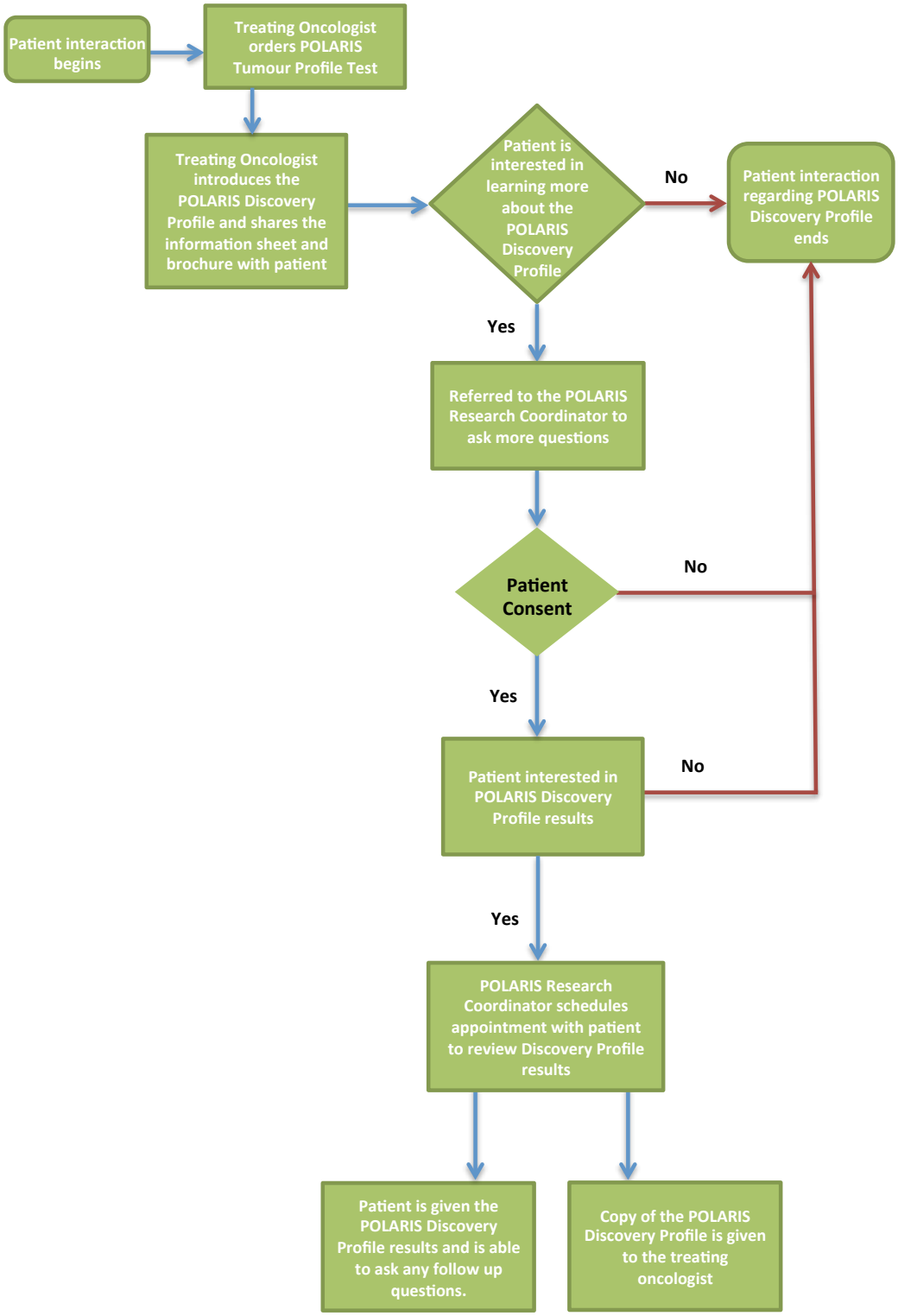
_____	_____	_____
Signature of patient	Name of patient	Date

_____	_____
Email (for results)	Phone Number (for results)

_____	_____	_____
Signature of witness	Name of witness	Date

_____	_____	_____
Signature of translator (if relevant)	Name of translator (if relevant)	Date

APPENDIX FOURTEEN: INFORMED CONSENT WORKFLOW



POLARIS Cancer Panel Consent Process