Genomics and Health: Personalized Medicine Program
Genome British Columbia

Genomics Applied to the Management of High-Risk Acute Myelodysplastic (AML)

SSH Sub-project
Clinical Genome Research in the Digital Age: Managing Informed Consent and Genomic Incidental Findings

RESEARCH REPORT

Genomics and Networks Analysis Lab
Simon Fraser University
Peter Chow-White
Anita Charters
Paulina Chow-White
Stephan Struve
Dung Ha
Eliot Tran
Amanda Oldring

May 15, 2014

Table of Contents

Summary of Research and Recommendations

Genome science is rapidly shifting from research labs and biobanks to the clinical setting. Doctors are beginning to utilize information from an individual's DNA for clinical decision-making and treatment. The AML genomic test from this project will potentially be the first time this new technology is deployed in Canada. The aim of the GE3LS project is to understand the opportunities, challenges, and risks for developing and adopting new genomic tests in the clinical setting. Many scholars', policy makers', and practitioners' intellectual work and policy guidelines have focuses on the genomic research setting and biobanks. Since the scientific goal is to bring a genomic test into the clinical setting, our research is forward looking to the clinical research and point of care settings. The issues we address are quickly developing in the diffusion of genomic technologies from the bench to the bedside. We conducted documentary and policy analysis and interviews with active BC genome researchers, policy, and decision-makers to explore the issues of informed consent, return of results and incidental findings at the point of care. We found the most pressing challenges for clinical genomics revolve around the process of gathering informed consent and the increasingly complex nature of returning results and managing incidental findings. The aim of this study is to provide information and analyses that can be used to improve the ethical and procedural guidelines and best practices for clinicians and point of care practitioners managing patient genome information. This information will also inform policy and decision-makers in government and the health care system. Our recommendations are synthesizing our empirical findings in conjunction with related international recommendations and guidelines.

Recommendation 1: Design a proactive informed consent process that addresses risks and benefits of digital genomic information

Recommendation 1.1: Emphasize the unique nature of digital genomic information and the Internet: Participant and patient documents such as consent forms and education manuals should include information and language about the potential digital pathways of their genomic information and the associated informational risks. Language should make it clear that clinical genomics generates digital information, which differs from a traditional understanding of the biological sample and can create new issues and challenges for maintaining privacy.

Recommendation 1.2: Respect clinical research participant and patient preferences and the right not to know incidental findings. Convey the scope of potential incidental findings and engage in shared decision-making process with the patient about what types of results may be returned. Acknowledge the potential to generate genomic incidental findings (GIFs) and the possibility of discovering findings that are presently unknown.

Recommendation 1.3: Contain language / disclaimer that privacy is not absolutely guaranteed. Provide details of data release and sharing, including potential public databases where data could be disseminated. Explain the potential of re-identification of anonymized data. Emphasize the digital nature of clinical genomic data and how this could impact issues of privacy and intellectual property.

Recommendation 1.4: Describe the data management and the potential for future third party use, such as researchers. This should include where and for how long both biological and digital samples will be stored.

Recommendation 1.5: Explain limitations to withdrawing patient/participant data from databases and that the participants *cannot* always withdraw. Explain that digital data is potentially indestructible; especially once it is disseminated in public databases and subsequently used by third parties.

Recommendation 1.6: Explain the social network nature of genomic information and explain the implications of familial issues, such as the return of test results to families of deceased, the disclosure of results to 'at risk family members' and/or other relevant parties, as well as the possibility of needs of family overriding objections of patients/participants. DNA is a unique identifier and can identify familial networks.

Recommendation 2: Return Results that have scientific validity and clinical utility
Results that have scientific validity and clinical utility should be returned in clinical research and point of care settings. This includes genomic incidental findings as discussed below.

Recommendation 3: Develop a 'green, yellow and red light' decision matrix

Recommendation 3.1: We recommend forming a group in British Columbia made up of clinicians, clinical researchers, genome scientists, and relevant stakeholders to decide on a decision-making matrix for managing the return of genomic incidental findings.

Recommendation 3.2: This group would formulate a management plan for return of research results. The matrix should consist of three classes of findings. 'Green' class findings have both scientific/clinical validity and clinical utility and should be returned. 'Yellow' class findings may have scientific/clinical validity but no consensus on clinical utility. These would be returned at the discretion of the clinical researcher or medical practitioner. 'Red' class findings do not have either scientific/clinical validity or clinical utility and should not be returned.

Recommendation 3.3: The information in the decision matrix should be made widely available to clinicians, practitioners, and researchers. Dissemination methods would include Internet resources such as a web page, social media, and mobile applications. For example, we envision Twitter could be used for real-time updates, and a mobile device app similar to 'Epocrates' could display and visualize most current classes of incidental findings.

Recommendation 4: Revise the decision matrix every year
We recommend revising the decision matrix every year due to the current rate of knowledge discovery and clinical validity.

Recommendation 5: Address the policy patchwork in British Columbia
We recommend a multi-stakeholder network be created in British Columbia to address the limitations of current healthcare and privacy policies, as well the potential need for new health information and data guidelines.

Introduction

Genome science is rapidly shifting from research labs and biobanks to the clinical setting. Doctors can now use the information from an individual's DNA for clinical decision-making and treatment. Information technologies, such as sequencers (which digitize DNA) and DNA databases (which store and manage digitized DNA data), are facilitating new insights into the human genome, enabling scientists to innovate genomic diagnostic technologies for clinical decisions. Many refer to these innovations as "personalized medicine", or the practice of using genetic information and other biological features to tailor health care to individual patients (Bush and Moore, 2012).

While information technologies offer enormous benefits for health care, they also present new issues and potential risks that challenge clinicians, scientists, and policy makers to reconsider common practices of clinical work and research. The AML genomic test will potentially be the first time this new technology is deployed in Canada and would mark the birth of clinical genomics in a national context. As science and technology studies scholars have shown, when a new technology moves from a small group of expert users into another context, in this case a population-wide health care system with a broad set of stakeholders and users, including patients and clinicians, new issues and practices arise (Hackett et al., 2008). While the large-scale analysis of patient genetic material would be valuable in terms of reducing costs to the health care system, it would also produce an abundance of individual DNA information (Caulfield and Knoppers, 2010; PHG, 2011; PCSB, 2012; PCSB 2013). As with all new technologies, it is critical to conduct research into the possible risks for individuals and groups and to consider whether appropriate measures could be introduced that would mitigate the potential for harm. Ideally, such an investigation should occur before a potentially disruptive technology gets disseminated more broadly. Otherwise, any issues that arise may put regulators in a reactive position that could severely constrain the new technology's uptake and marketability. Unlike the explosive expansion of the Internet due to popularization and commercialization, there is an opportunity to shape the adoption of diagnostic genome technologies to be practically useful and socially and ethically sustainable.

In this project, we examined opportunities, challenges, and risks to different stakeholders in clinical genomics generally and, specifically, to the development of a genomic test for AML cancer. We identified new issues in the clinical-research and clinical community, such as how to manage genomic incidental findings, clinical research, and point of care settings (Wolf et al., 2012; McGuire et al., 2013; PCSB, 2013; Senecal et al, 2013; Wolf, 2013). In consultation with our collaborators, the literature, and the Scientific Advisory Committee's (SAC) guidance, we focused our research on investigating best practices in a clinical setting for managing informed consent, return of results, and genomic incidental findings. We also explored the regulatory frameworks that will govern the handling and management of genome information in British Columbia's clinical and care networks. We addressed the following overarching research questions: What are potential social risks from the genome information produced by genome sequence analysis for diagnostic assessment that may affect individuals and groups? What is the current regulatory environment in British Columbia and Canada that would govern the management of individual genome information in the context of personalized medicine in clinical contexts? What are the emerging policy debates, if any, that would impact the deployment and use of this new technology?

The aim of this study is to provide information and analyses that can be used to improve the ethical and procedural guidelines for clinicians and point of care practitioners managing patient genome information. This information will also inform the government, health care system, and citizens about the rapidly changing landscape of personal genomic technologies as they transition from research to clinical practice.

We found the most pressing challenges for clinical genomics revolve around the process of gathering informed consent and the increasingly complex nature of returning results. In our review, we examined the ethical and pragmatic issues surrounding clinical genomics, specifically new challenges that arise in the translation of genomic technologies from the research bench to the clinical bedside. Primarily, we hone in on the practical and ethical issues involved in informed consent and returning research results. We focus our research on the local context of the development and deployment of new clinical genomic technologies and the regulatory context in British Columbia, Canada.

In the policy environment, we found that although many regulations and guidelines exist, the state of best practices is uncertain. Unresolved issues include re-identification of anonymized samples, determining effective privacy protection measures for downstream data, and creating effective processes of informed consent to allow scientists and clinicians to realize the full potential of genomic data while still respecting participants' privacy and autonomy. Unresolved issues also surround the dissemination of research results and incidental findings such as what to return, who should return, who is liable, and if results should be returned to family members.

The Nature of Genomic Information: Personal, Social and Digital

The Internet plays a significant role in clinical genomics as both a risk to individual privacy and a benefit to the development of genomics in personalized medicine and the management of patient information in the healthcare system. However, most stakeholder discussions fail to address the role of the Internet and information technologies. We also found a deficit of direct references to the Internet and information technologies in informed consent documents and patient education manuals. Clinical genomics is establishing itself within the larger context of Internet culture creating unique barriers as well as possibilities that are often ignored in stakeholder discussions. If the promises of personalized medicine come to fruition, then genomics will be a disruptive technology with wide reaching impacts on health care. In comparison, the Internet is also a disruptive technology that has deeply impacted arguably every social institution and transformed the way that we operate our institutions and organize our daily lives. In the Web 1.0 era, Internet users could view information but not easily contribute online content. The advancement to Web 2.0 has changed this context dramatically. Users are now both audience and authors while social media has changed the notion of privacy. We increasingly live our lives in public. Further, old laws do not recognize how unique DNA and associated genomic data is and how it is different from a person's emails, demographic information, and general health status. Scientists have pursued an open access model to genome information since the 1990s. This benefit to the scientific community has increasingly become a risk for individuals because of advances in computer algorithms and database linking technologies. In short, big data has made it easier to re-identify individuals in databases. Genomic data has the potential to reveal information about future health status of the donor individual as well as her family members creating a new category of privacy concern. Clinical genomics is developing in this new communication context yet is being governed by laws that were written in a time when big data and this category of privacy concern did not yet exist. Clearly, it is time to re-examine how clinical genomics is being governed and identity if concerns due to new information technologies are being addressed.

Genomic data is unique personal information

Advanced genomic technologies such as whole genome sequencing (WGS) generate an increasing amount of personal and potentially clinically relevant data. This clinical genomic data contains identifiable information, which requires informed consent and has to be anonymized

(Cheung et al., 2013). The key issue for ethics review boards centres on identifiability and privacy. Research participants and patients are only required to give consent if the sample is deemed identifiable. However, different policy and legal frameworks have varying definitions of what constitutes 'identifiable information'. In fact, already existing data that cannot be readily identified to involve "human subjects" might not even require a human ethics certificate. Conversely, to comply with the US Freedom of Information Act (FOIA), the National Institutes of Health (NIH) determined that releasing DNA violates personal privacy (McGuire & Beskow, 2010). Clearly, regulations and best practices are still in flux concerning non-identifiable data. Regulatory bodies will have to create rigid but practical decision-making structures to guide clinicians in this crucial transition from genomic research to clinical genomics (Black et al., 2013, Burke et al., 2013; Dorschner et al., 2013; Fernandez et al., 2013; Wolf, 2013; Miller et al., 2013; Middleton et al., 2014).

At the federal level, the tri-council agencies CIHR, NSERC and SSHERC have policies by which funded researchers must abide. The Government of Canada Panel on Research Ethics released a 2nd edition of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2) in 2010 and thus updating the first edition from 1998. The changes in the second edition reflect the immense influence of genomic research in Canada's health research. Guidelines for human genetics were updated and new guidelines for information security and incidental findings were included. Further, the newly edited policy guidelines clarify requirements for informed consent. These changes mirror ongoing debates of issues related to genomic research such as informed consent and return of research results occurring in the literature. While these issues remain somewhat vague in legal texts, they have very concrete barriers in the clinical practice.

The genome is an individual identifier *and* a familial network identifier

The social nature of genomic results and its relevance for other family members challenge clinical practice. Boddington (2010) examines ethical components in genomic data with regards to valuing the autonomy of one person over another (participant versus family member). Genomic data presents challenges for medical research ethics in that it generates data relevant to relatives of the participant. Data can reveal attributes other than health such as physical and mental traits as well as ancestry insights. This raises questions separate to those related to physical harm; issues of privacy, confidentiality, and rights to information. The current debate is whether or not relatives of research participants should be considered data subjects, and if so, what circumstances would necessitate a requirement of obtaining consent for participation. Balancing autonomy of participants with that of their family involves discussing all risks and aspects of the project that may affect the family. Further, some suggest encouraging the participant to discuss his or her participation and its implications with family members (RMGA, 2013). The literature is unclear as to who should take the responsibility of involving family members and often simply recommends seeking genetic counseling or moving this task to a clinician.

Genomic research results carry unsettling notions of relatedness and dealing with socioculturally defined ideas of family and kinship. Francke et al. (2013) demonstrated, for example, how beneficial BRCA mutation tests were to participants and lead to "a cascade effect as relatives of newly identified carriers also sought testing and more mutation carriers were identified (p.1)". Additionally, beliefs about risk may actually follow social ideas of family rather than biological. Hence, it is impossible for the investigator to predict how family members would react to clinical results because the understanding of risk is a complex process. However, simply passing the responsibility to the participant or patient may not be appropriate. It may be most effective to enhance the participant's ability to discuss the issues with family members by providing educational tools (Boddington, 2010).

Policies and regulations do not provide clear guidance for disseminating results to family members. The TCPS2 principle of autonomy would dictate that participants should control the process of sharing results but exceptional circumstances requiring disclosure - such as a serious or life-threatening[1], preventable and treatable disease - should override this principle (TCPS2, 2010). The United Nations International Declaration on Human Rights recognizes the right to know by all involved but does not specify how results should be handled when the family has not expressed a preference. The Human Genome Organization (HUGO) emphasizes the importance of genetic information to the family but does not stipulate how or when the family should be informed. The International Pharmacogenetic Working Group acknowledges the conflicting advice about returning results to the family yet recommends respecting the privacy of the participant. They also recommend the informed consent process should identify who will have access to the information (Black & McClellan, 2011). This question of access seems manageable on the surface, which is deceiving.

Genomic data are digital information.

Information technologies, such as sequencers and DNA databases, are critical infrastructure for clinical genomics. They facilitate the transition from analog samples to digital code. Biological material which is stored and processed centrally in one location transitions into digitized data which are collected in decentralized, possibly public databases. This shift into the digital realm of binary code and secondary research makes safeguarding privacy of personal genomic information infinitely more difficult, if not even impossible. The collaborative nature of genomic technologies entails that different types of stakeholders and collaborators can use sequence data across regions, and hence downstream protection of privacy is vital to ensure the protection of personal information. This very practice of downstream analysis involving secondary use of genomic samples and resulting digital pathways challenges practices of safeguarding privacy and autonomy at its very core (TCPS2, 2010).

Even the highest standards of protocols are not impenetrable and privacy can still be breached (see Homer et al, 2008). Arguably, researchers and clinicians would have to go to great lengths and statistical sophistication to re-identify previously anonymized samples. However, the issue we want to raise is not particularly how personal genomic information has been or could be re-identified, but rather that it *can* happen, and that the digital pathways for re-identification appear to broaden.

Moreover, genomic information develops a digital life on its own. A number of scholars and practitioners recommend that participants have the ability to withdraw from clinical research (Burke et al., 2013; Middleton et al, 2014,); however, the digital pathways of genomic research, such as databases and repositories, render personal genomic information uncontrollable for the participant and ineradicable in its nature. As a consequence, one could argue that patients and participants lose the ability to withdraw from clinical research altogether. This limitation of the withdrawal process will need to be addressed in consent forms and patient educational material (PEM).

The above mentioned questions and issues around the nature of genomic results profoundly impact the principles for returning results.

[1] The term 'life-threatening' is vague and open to interpretation. For reasons of clinical utility and decision-making management, further guidelines of what constitutes a life-threatening condition should be established.

Informed Consent: Communicating Benefits and Risks of Digital Genomic Information

Perhaps the most prominent implication of the intersection of genomic and information technologies has been the reconfiguration of the meaning of informed consent and privacy in the digital age. As genomic technologies such as WGS generate more individual data than before, issues of informed consent, clinical validity, and the ethics of returning results become increasingly pressing (Caulfield and Knoppers, 2010; PHG, 2011; PCSB, 2012; PCSB 2013) .

The North American research principle of respect for persons enforces the moral obligation to respect human autonomy[2] (TCPS2, 2010). The key requirement to autonomy is the informed consent of human participants. It must be based on the most possible complete understanding of the clinical purpose, the ethical protocols, and the risks and benefits to the participant and to others. Obstacles to exercising autonomy include inadequate information or understanding, lack of freedom to act from controlling influences, and inaccessibility to resources or knowledge.

The informed consent process can be traced back to standards outlined in the Nuremburg Code, Declaration of Helsinki, and Belmont Report. Informed consent recognizes an individual's right to autonomy over their intact physical body and right to privacy and confidentiality over identifiable health information (Cheung et al., 2013). This concept of autonomy has transformed biomedicine in North America; however, debate exists regarding its effectiveness for protecting privacy. For example, a participant or patient signs an informed consent form agreeing to the terms of use of a particular sample. The institution may fully intend to honour the agreement; however, privacy can still be breached. Because the data may be stored and potentially used by other practitioners in various forms, downstream protection of privacy is vital to ensuring autonomous decisions are honoured. When personal data is lost or leaked, the problem is carelessness in downstream processes, not consent. Some research ethics boards waive informed consent requirements when the only potential harm is loss of privacy—when reasonable privacy protection is in place (Taylor, 2008).

Safeguarding Privacy

The bioethical model positions anonymization and informed consent as two sides of the same coin. The TCPS2 chapter on privacy and confidentiality stipulates that an important aspect of privacy is the control of information about oneself; this includes control over personal information by giving or withholding consent for collection, use, and disclosure of information. Thus, investigators must secure and protect information using physical, administrative, and technical safeguards. The first and easiest way to safeguard personal information is to anonymize data by stripping all direct identifiers; however, this may not be ideal as new data from an individual cannot be added to the dataset and results cannot be returned to individuals for clinical utility. The second and next best alternative is to code the data so that identifiable information can be re-linked to the data. Of course, the key to the code must be safely guarded, ideally by a third party. The remaining third alternative is to keep the data in its original identifiable form but de-identity it as soon as possible. The principal investigator of a project or the clinician of a patient is usually the custodian of the data. All three methods still have risk for re-identification (TCPS2, 2010). Because of the realization of the risks from potential re-identification, the United States has two mechanisms of protecting privacy. First, Certificates of Confidentiality can be issued by the federal government to protect identifiable research from forced disclosure in a legal proceeding (although not a criminal case). These have rarely been tested and cannot replace policies for data protection and security. Second, the US federal law

[2] Autonomy refers to being free to make a decision without interference.

Genetic Information and Non-Discrimination Act (GINA) prohibits discrimination in health coverage and employment based on genetic information. This does not, however, cover life, disability, or long-term health insurance (McGuire & Beskow, 2010). Canada does not yet have such an act—so there is little protection for Canadian research participants from the risks of re-identification of their sequenced DNA, such as in the landmark work of Niels Homer and his team in 2008.

Updating The Concept For Clinical Use

It becomes clearer that the standard concept of informed consent has to be revised. Some have suggested that the fundamental principle is not effective for genomic medicine (PHG, 2011; Henderson, 2011). The traditional informed consent process may not effectively allow investigators and clinicians to realize the full potential of their patients' data; may not adequately inform patients/donors about the benefits and risks of their DNA information becoming digital information, which may be disseminated; nor adequately cover the scope of known and potential incidental findings (PCSB, 2012; PCSB, 2013). Issues of balancing broad enough consent to make data useful while still protecting the privacy and confidentiality of participants remain unresolved. Developments in clinical genomics should go hand-in-hand with changes to the informed consent process to reflect patients' preferences for data sharing of their genomic sequence and derivatives. Concerns have been raised that giving patients control over decisions about data sharing will lead to excessive anxiety about protecting privacy and reluctance to share data and thus negatively impact clinical practice. Different types of consent exist and debate ensues about which type is most effective for genomics studies. McGuire et al's (2011) study of three different types of consent (traditional, binary and tiered) - each with a different level of control over the decision about data sharing - demonstrated that tiered consent maximized autonomy because participants were able to choose their preferred data sharing preferences (McGuire et al., 2011). As the issue of identifiability is key, different types of consent forms exist to reflect different possibilities of re-identification of data.

Secondary Uses and Three Types of Consent

Using stored tissue samples for future secondary research[3] challenges informed consent in its own way. A tension exists between individual and societal interests. A loosening of current regulations has to balance potential benefits and donors' rights as research may erode privacy and confidentiality, be offensive to groups, and enable discrimination. In Canada, the Personal Information Protection and Electronics Act (PIPEDA) allows personal information to be used for statistical or scholarly research without consent as long as certain conditions are met.

Biobanks store tissue for future genomic studies. However, it is difficult to obtain an effective consent form from biobank donors because it is impossible to predict future secondary uses (Secko et al, 2009). Like GWAS datasets or sequenced genomes, biobank samples can become the subject of an infinite amount of further clinical questions and transform into myriad types of data. It is impossible to identify all potential future uses at the time of consent, which has caused other types of consent to be examined. This issue can be examined in the very pal-

[3] This concept can also be considered Biobanking. Biobanks are repositories of blood and tissue combined with medical and other personal information. Tissue samples can be used for many different purposes including having genome sequencing or SNP analysis performed. The results are then studied in context with information about the sample donor. The goal is to untangle links between genetics and environmental factors to understand causes of common diseases.

pable example of the legal challenge against the Provincial Health Services Authority (PHSA) for retaining newborn blood spot samples and allowing further secondary research on those blood cards (see L.D. v. Provincial Health Services Authority, 2012 BCCA 491). Not only can these legal challenges shake public trust in the biomedical system, they can also drastically impact the utility of Canadian newborn metabolic screening processes (Barr, 2010).

As a result, possible changes can be made to the consent process, such as focusing on *broad consent* or *multiple requests* over time. Both options have drawbacks. While broad consent could be too vague to be meaningful (Secko et al, 2009), seeking to re-consent and re-contact individuals for each new research use can violate privacy and cause anxiety to the individuals. Because genomic research benefits future patients and society as a whole, it has been argued that using archival tissues is justified even without consent. Ethical guidelines dictate that these samples have to be anonymized, which could decrease their scientific value. This process makes data validation very difficult and obstructs longitudinal data as samples cannot be associated. Further, decisions made by donors may lose influence as their samples are de-identified and therefore separated from any sample information or opportunity for re-contact (Bathe and McGuire, 2009).

A third type of consent model - *the informed cohort* - could address these issues. This model keeps participants involved in the research process: after providing a bio specimen for sequencing, participants can subsequently use a Web-based personally controlled health record to give feedback to the researcher. Participants can decide if they want to receive feedback about their health, such as newly discovered gene variants which may be relevant to them, and what to disclose to their health providers. A risk report is created using lab-analyzed data and feedback from the participant (Kronenthal et al., 2012). The informed cohort model is similar to that used by direct to consumer (DTC) genomic companies such as *23andMe*[4]. Because of these methods, DTC genomic companies may have access to sequenced data along with longitudinal data, which could provide increased clinical utility for customers[5]. Currently, the principle to safeguard privacy overrules the demand for clinical utility.

Anonymization

It appears that anonymised or de-identified samples are the best method of protecting privacy. However, the principles and drawbacks of such samples are under debate in the literature. For Biobanks, Bathe and McGuire (2009) suggest that:

- Ethics committees must balance relative benefits and risks of the research project.
- Source data files should not be anonymized; they should be coded and protected by encryption and file protection.
- If potential harms and privacy risks are assessed to be minimal and re-consent is impractical, a waiver may be granted.
- Minimal risk is achieved when samples and data shared in a database are restricted to approved researchers with a legitimate research purpose. Data requests should be reviewed by an independent review board and investigators should agree to protect donor privacy, maintain confidentiality, and respect any choices made in prior consent forms.

[4] 23andMe customers submit a sample of saliva for sequencing and are encourage to fill out surveys and questionnaires over time regarding their individual lifestyle and health.

[5] The blurring lines of customer and research participant has been addressed in the literature (Tobin et al., 2012). If DTC customers are classified as research participants, these companies may have to abide by stricter consent requirements and undergo regular ethics reviews.

These suggestions are similar to the regulations the TCPS2 guidelines for GWAS databases, such as recommendations for the consent and secondary use of existing samples. The consensus appears to be moving toward 'looser' rules where consent can often be waived.

McGuire and Beskow (2010) outline seven common features of genomic research and their implications for informed consent. In summary, the traditional model of consent may have to be re-evaluated as genomic medicine evolves. Alternatives such as *tiered consent* forms or the *informed cohort model* may address issues of respecting autonomy and the difficulty of re-contacting donors of archived samples. Genomic research holds great promise, but it requires a policy framework that effectively respects the core ethical principles for treating human participants while allowing researchers to access and use data which is vital in addressing their research questions. This dichotomy is mirrored in many policy documents which acknowledge that the intellectual endeavour of genomic technologies has to respect autonomy and privacy (PCSB, 2012; PCSB, 2013).

To summarize, current concepts of privacy no longer seem to fit the genomic age. Genomic results are digital information that are easy to share and difficult to protect. What we have demonstrated is that it is increasingly technologically impossible and/or ethically irresponsible to offer participants and patients unequivocal assurance of privacy when asking to use their genomic data in the kind of large-scale genomic databases that will guide genomic research and clinical genomics.

Returning Results in Clinical Research and Care Settings

To return or not to return? That was the pivotal question when we set out to examine the return of genomic results. However, over a short span of time the intellectual and ethical terrain has shifted. The applied care setting of clinical genomics replaces this binary dilemma with the unequivocal medical assurance to return results under ethical parameters (ACMG, 2013). Looking forward, bioethicists, clinicians and doctors have to face the questions of what will be returned, who communicates genomic results, where this return will happen and how exactly it will happen. Addressing these questions will pivot the discussion towards the very applied healthcare context of clinical genomics.

The biggest challenges of returning results hinges on the complex nature of the clinical setting and genomic data. The return of genomic tests raises ethical questions around beneficence and autonomy, as well as privacy. Moreover, it elevates practical issues, such as patients' trust in the biomedical setting, bottlenecks in the system, or pile-on effects in the care spectrum (PHG, 2011; Zawati & Knoppers, 2012) or research setting (Black et al., 2013).

As for clinical research, there are two types of research results returned by investigators: 1) *general research results* which are generalizable to a group, often confirming a research hypothesis such as a genetic variant linked to cancer; and 2) *individual research results* which are directly associated with an identified individual. When information is discovered which is not linked with research objectives or hypotheses, it is considered an *incidental finding*. These have unique issues that are discussed in the next section. *General research results* are normally shared without much controversy but debates continue with regard to returning *individual research results*. Past studies have identified situations where return of research results must or may occur if 1) results are accurate and 2) results are relevant to the health of the recipient (see RMGA, 2013; ACMG, 2013). Returning research results may be encouraged by the Respect for Persons' principle (described above) since it avoids treating persons solely as a means to an end. Returning results may also be supported by the two remaining overarching principles: concern for welfare and justice (Levesque, Joly, & Simard, 2011).

Returning general results is clearly the obligation of the investigator in order to adhere to the three core principles of the TCPS2 (RMGA, 2013); however, returning individual research results is still under intense debate. Clayton and McGuire (2012) argue against returning indi-

vidual research results. They conclude offering individual results may encourage therapeutic misconception: believing research participation can or should provide personal benefit (Zawati & Knoppers, 2012). A vital difference between research testing compared to clinical testing is that research testing does not meet laboratory requirements or standards. Beneficence-based obligations are role specific and debates continue as to whether investigators possess such obligations. For instance, physician-scientists may have such an obligation but imposing this same responsibility on researchers may open the door to increased liability.

More importantly, returning research results would require samples to be re-linked with their identifiers. Much research data is anonymized (as recommended by TCPS2) and therefore returning results is not an option. Further, samples in consortia, such as the International Cancer Genome Consortium (ICGC), are often sequenced by one research group and then analyzed by another. Secondary researchers then use the analyzed data for their research purposes and have agreed not to attempt to re-identify individuals from the samples. If a secondary researcher discovered a clinically important result, it would be very difficult to inform the individual. Thus, it has been suggested that international consortia could adopt the practice of having a committee that reviews results from secondary researchers and then works with experts to determine if a result should be returned (Wallace, 2011).

Evaluating Research Results

Regardless of the origin of a result, it has to be evaluated before it can be returned to the individual. Levesque, Joly, and Simard (2011) propose a framework for determining whether an individual research result should be returned. It is based on the ACCE model (Figure 2) and states that results should be evaluated on four criteria:

- Analytic validity: how accurately and reliably it measures the results
- Clinical validity: how consistently and accurately the test can detect or predict outcomes
- Clinical utility: how likely the result may significantly improve health or health related decisions made by the participant
- Ethical, legal, and social implications (ELSI)

They conclude that results should not be returned if a test is difficult to interpret and/or the condition is benign. In addition, results should only be returned if tests are accurate and treatment is available. Even if participants wish to have all results disclosed, Clayton and McGuire (2012) argue that participant demand is not a sufficient justification to oblige the investigator to offer results in a research context. In the clinical context, patients tend to have more rights to their health information and clinicians have ethical obligations to address any relevant health information. Because the results were likely not validated and not generated in a clinical care situation, the participant does not have the right to demand the results. Returning results could actually be prohibited by the Clinical Laboratory Improvement Amendment (CLIA) (Clayton and McGuire, 2012). To even consider returning a result, it must be evaluated by a model such as the ACCE so that its clinical and analytic accuracy are guaranteed and all ethical, social, and legal implications are discussed. The benefits must outweigh any risks to return results (see RMGA, 2013; Francke et al., 2013, ACMG, 2013)

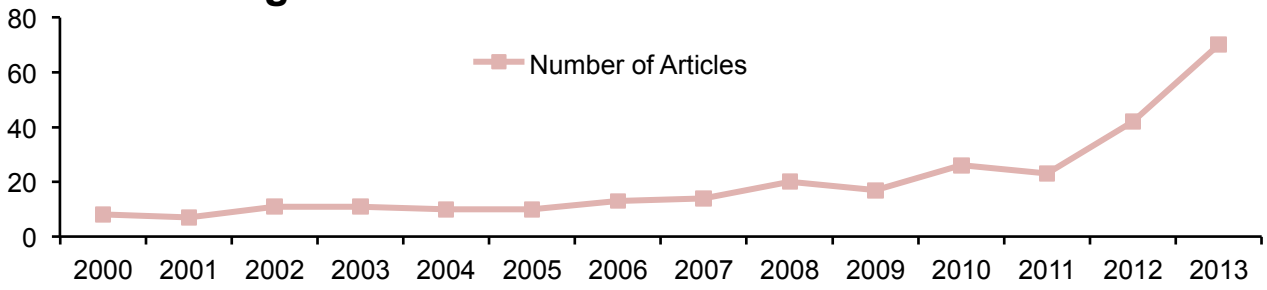
The TCPS2 (2010) states, “In some cases, genetic research may reveal known gene-disease associations or other information, including incidental findings, that may be clinically relevant for individuals (or their biological relatives) in treating or alleviating health conditions or risks. In other cases, research may reveal information that is inconclusive, in its scientific, clinical or other implications (p. 182).” The TCPS2 does not give recommendations about which, if any, results to return. It does, however, illustrate some of the potential risks including: 1) possible need for follow-up clinical testing and counseling, 2) potential implications for biological rela-

tives which may raise disclosure considerations, and 3) possible effect on employment or insurance. Thus, the TCPS2 requires the investigator to create a plan for managing genomic information and to consider all relevant risks and benefits. These plans "may include sharing individual results with participants, notification of general, non-identifiable research results through newsletters, websites or other means (TCPS2, 2010, p.183)". Interestingly, the TCPS2 does advocate for the autonomy of the participant and states the investigator shall give participants options for receiving or refusing different types of information. Further, participants can express preferences about sharing information with family members although some situations may require investigators to disclose information to third parties (TCPS2, 2010).

Incidental Findings In Clinical Setting

The issue of returning incidental findings has reached a watershed moment. When we reached the end of our review of relevant literature, the topic of incidental findings had already topped the scholarly and public agenda (Figure 1). The latest count is equivalent to an increase of 875 per cent.

Figure 1: Genomic Return Research Results



A number of groups in Canada, the UK and the US have released major policy reports on the issue of addressing incidental findings in clinical research and care (ACMG, 2013; PHG, 2011; PCSBI 2012; PCSBI, 2013). The main trend among the recommendations is to return results and incidental findings in an ethical and clinically responsible manner consistent with professional norms and local practices. Some have also pointed out legal issues that are involved in returning incidental findings (Evans, 2013). Clayton et al. (2013) reviewed 8 legal cases from medical imaging involving incidental findings and concluded, based on precedents set, that clinicians could be held liable for not returning genomic incidental findings (Burke et al., 2013; McGuire et al, 2013; Wolf et al., 2012). Liability would also include not returning genomic incidental findings to either the patient or another clinician, or from failure to refer the patient to a clinician with greater genomic expertise.

Genomic Literacy

Most clinicians presently have little to no ability to interpret whole genome or exome sequencing data and would consequently be reliant on reports from the laboratory or external sources (Baars et al., 2005). A recent survey of 329 BC physicians unearthed that although the vast majority considered genomic knowledge clinically relevant, "67.8 % assessed their own knowledge of genomic technologies as very poor or poor (1 or 2 on a 5–point scale), and 64.6%

rated their own knowledge about how to incorporate genomics into clinical practice as very poor or poor" (Friedman, 2013). It can be argued that rapidly evolving genomic technologies challenge the growth of knowledge and genomic literacy among physicians. Therefore, complex protocols will have to be established to guide clinical decision-making processes based on accurate and clinically useful results if incidental findings are to become clinically useful.

Genomic technologies push forward into clinical practice. In an effort to increase genomic literacy among clinicians, regional clinical programs should be modified to include stronger genomic components. While the institutional education of BC's doctors is currently "almost completely devoid of content related to genomics" (Friedman, 2013), Jan Friedman is advocating that UBC's Medical curriculum should include stronger genomic components to "improve the ability of future physicians to use genomics appropriately in their medical practices" (ibd.). Mirroring this call, a group of experts in BC is already embracing a more inclusive approach to genomics. A local group of clinicians and oncologists, the Personalized Onco-Genomics Project, uses the sequencing expertise from the GSC and BCCA to interpret the WGS data for clinical use.

ACMG Recommendations

The American College of Medical Genetics and Genomics (ACMG) released their highly anticipated recommendations for reporting of incidental findings on clinical exome and genome sequencing in March 2013. A working group drafted this report after a year-long consensus process that included review by outside experts. This report focuses on clinical sequencing ordered by a clinician for the purpose of diagnosing a specific condition in a patient. A positive result (pathogenic alterations in gene(s) relevant to the diagnostic indication) would be considered a primary finding. An incidental finding would be a positive result for pathogenic or likely pathogenic alterations in genes that are not known to be relevant to the diagnostic indication but were deliberately searched for by the laboratory.

The ACMG working group acknowledged the lack of evidence concerning the benefits, risks and costs of disclosing incidental findings; however, they determined certain incidental findings would likely have medical benefits for the patients and families receiving clinical sequencing results. The working group created a minimum list of incidental findings to report to patients. They estimate 1% of sequence reports will include an incidental variant from the list. This list is largely composed of conditions where secondary tests are available to confirm the diagnosis of disorders with preventative measures or treatments prioritized. The working group did not recommend reporting findings that were discovered but had not been intentionally searched. The expectation is for the ordering physician to explain the report and contextualize the results with the patients' personal and family history, physical examination, and other relevant findings.

The working group raised the concern that negative incidental findings in a report could be misinterpreted as a confirmation of the absence of a pathogenic variant. They recommended including language in the report to differentiate the quality between primary and incidental findings. For instance, primary findings were likely confirmed by a secondary method in the laboratory. They recommend that laboratories should review literature and databases of a pathogenic incidental finding which would require significant manual curation. Patients receiving these incidental findings reports would have to undergo a comprehensive genetic counseling process for numerous conditions unrelated to their primary indication for sequencing. However, the working group did not favour allowing the patient to have preference concerning which findings to be reported to them. They recommend all findings to be disclosed by the clinician to the patient. They acknowledge this appears to violate the patient's autonomy but felt clinicians and laboratory personnel have a fiduciary duty to prevent harm. Further, the working group did not limit this recommendation by age since they felt a child's right not to know does not supersede the par-

ent's opportunity to discover a life-threatening risk. Of course, the patient (or family) can decline clinical sequencing if they feel the risks outweigh the benefits.

Other Issues

Clayton and McGuire (2012) explain how individuals are naturally curious about the possession of information held by another person which pertains to them—this is labelled involuntary curiosity; however, statistics on screening tests show people often choose not to undergo screening or predictive testing when they have a choice. Currently, clinicians do not yet have the responsibility of monitoring every aspect of a patient's health on a continuous basis. Medical care is given in response to symptoms or age appropriate issues. A paradigm shift would have to occur whereby physicians are ordering tests for all available diseases which are diagnosable through an incidental findings report. Clayton and McGuire (2012) warn, "One thing is certain—if these practices become routine, they will be legally required. This is the way tort law has worked for decades (p. 479)."

In summary, as with informed consent, many issues remain regarding returning genomic results. Currently, research results, including incidental, are unlikely to be returned as most samples are de-identified and not likely validated. Researchers may even violate consortia or funders' regulations if they attempt to contact an individual. Participants in research may want results, but this alone does not provide an argument to return results, especially if it affects biological family members. Clinical results are very different. Primary results are validated and are returned as part of clinical care. The ACMG report on incidental findings is just the beginning of a discussion which will continue until effective and acceptable policies are determined. Currently, clinicians and physicians practice medicine by evaluating symptoms and consequently ordering tests to confirm their diagnosis. If clinical sequencing becomes routine, returning incidental findings would drastically change the practice of medicine. It is still unclear when, or if, medicine will fully embrace genomic sequencing; further, policies regarding what to return and how to return results must be incorporated into the medical system for such a change. Much more debate will likely ensue until routine personalized medicine is a reality.

Conclusion: The Jolie Effect

Some scintillating conversations around genomic testing have started in the public sphere. Last year's headlines of Angelina Jolie's double mastectomy highlights the agenda-setting function of the mainstream media, but it also demonstrates that undergoing genomic testing affects more people in the social network than just one patient. Jolie's opinions raised awareness for genomic testing, but they could have done a disservice to genomic research by possibly swaying public opinion towards perceived anxieties about finding out risk factors for disease (Borzekowski et al, 2013; Kamenova et al, 2013).

This perceived anxiety covers just the tip of the genomic iceberg. It represents what we call the 'Jolie Effect': a public discussion that is rightly raising awareness for genomic issues yet focuses on topics that are too narrow to capture the issue's full scope. What we have to keep in mind is that Jolie's genomic test was likely limited to just the BRCA1/2 gene. It was conducted in standard clinical care, which means the result can be returned. But what if the laboratory had tested other genes, such as those recommended by ACMG? In that case, Jolie might then have to learn about other risk factors hidden in her genes. Any consent form she may have signed for her clinical sequencing would become important for protecting her privacy. What if her genome was uploaded into a public database for future secondary uses or stored in a biobank? The single-nucleotide polymorphisms (SNP) a celebrity possesses could be of great public interest.

This example demonstrates the current blurring of research and clinical care. Jolie's sample was taken in a clinical context and is unlikely to enter the research world. However, the

hospital could eventually release some of her tissue from her mastectomy after the archival period. What consent forms would protect her then? More policies and regulations are required to clearly distinguish guidelines for research and clinical samples so that genomic testing and sequencing can bring the promise of personalized medicine to fruition.

Methods

Our interviewee population consisted of active researchers and policy and decision makers in BC. Our goal was to understand how this population understands the concepts (Kvale, 2007), processes, and practices related to clinical genomics. We sought to identify individual, laboratory, and project processes (including informed consent protocols and policies on returning research results), institutional practices (such as re-identifying anonymized data), and knowledge of British Columbia's research practices and guidelines (especially related to issues of incidental findings and returning research results).

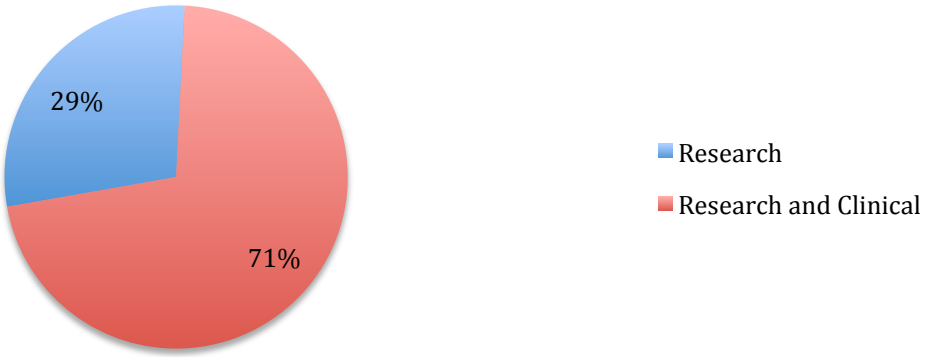
Sample Selection

The sample selection of active BC researchers was difficult to identify as we discovered a 'weak' and loosely connected network in BC. We built a database of 214 stakeholders and divided them into 2 sub-categories: 1) General Stakeholders Assorted, and 2) Active BC Researchers. We then used data-linkage techniques to identify a subgroup of researchers and clinicians actively working on genomics in BC (and nationally). This data combined information from recent applications to Genome BC and Genome Canada applications. From this process we identified a list of 98 active BC researchers. From this list, we contacted 67 to request an interview via e-mail, and were successful in interviewing 36 people. Additionally, we interviewed seven policy officials[6].

Interview Process

The interviews were semi-structured based on our interview instrument which was developed and tested during the initial pilot interviews. The interview protocol and procedures were conducted under REB regulations of Simon Fraser University. The majority of the interviews were conducted face-to-face; four interviews were conducted over the phone when a face-to-face situation was not possible. When the interview was completed, the researcher would go over the notes and make annotations for issues and items that could be addressed in subsequent interviews and/or analysis. After having them transcribed verbatim, the interviewer checked the transcripts against the recordings for accuracy.

Figure 2: Scope of Respondent Activities



[6] See list of interviewees in Appendix 3.

Data Analysis

Quantitative data analysis involved turning words into numbers to understand general trends and inform qualitative analysis and recommendations about best practices. The process involved two individuals coding independently to ensure a high level of intercoder reliability. A team of four researchers developed content categories using an iterative process of reviewing data and literature, which was subsequently tested and validated. The team discussed any discrepancies encountered during coding. When disagreements could not be resolved, the coders consulted the principle investigator to develop a consensus.

Qualitative analysis was conducted using a coding schedule, which was constantly being refined in an iterative fashion. The researcher used a qualitative analysis program, *NVivo*, to code the interviews. She coded six main sub-sections first: 1) informed consent, 2) return of research results, 3) incidental findings, 4) governance, 5) the Internet, and 6) blurred lines between clinical and research environments. Further coding was necessary until the response had been categorized sufficiently, usually on no more than three levels. After identifying a broad number of sub-codes, she refined them, merging similar codes and eliminating some if there were fewer than three responses to the code. In creating a report outline, she looked at what was said, how it corresponded to the literature in the area (or not), and then developed report sections that would correspond to both the literature and the data.

Resultant themes were then presented to the team and project leader for review and discussion. Agreed upon themes were then further examined in detail and conclusions made. Key areas as determined by the literature are discussed in this report including informed consent, return of research results, and incidental findings.

Results and Findings

After preliminary data analysis and literature review, we focused our in-depth coding and analysis on three main areas: informed consent, return of research results, and incidental findings. Our interview protocol asked direct questions about these three areas enabling the gathering of information on a wide variety of practices as well as opportunities, risks, and challenges regarding these areas. Over half of the interviewees (57%) use whole genome sequencing in their projects and all used genomics in their research and/or practice.

Informed Consent

Type of Consent

We asked active BC researchers about their consent protocols and procedures. Each active BC researcher uses an individual decision making process for type of consent indicating there is no standard. Clearly the process of obtaining Research Ethics Board approval has an impact as one interviewee states,

> I make [the consent type] tiered but the initial consent is blanket because it is too much hassle to get it through the REB (Interview 1008).

The consent projects using whole genome sequencing tends to be broad but respondents emphasize how restraints do exist on the resultant data such as being limited to a type of research (i.e. disease specific). One interviewee explains,

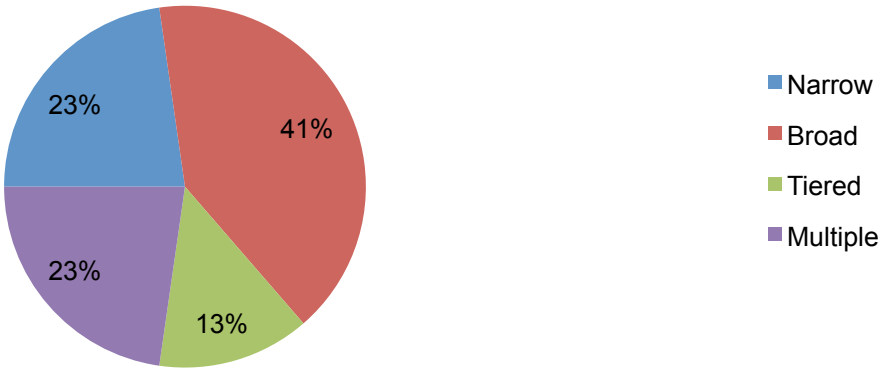
> We usually have a very broad thing that we say we will use the material for genomic research related to lung cancer, for example. Because it's hard to predict what information will come out of it in the future (Interview 1014).

Of course, many clinical studies are focused on a specific hypothesis allowing the consent form to be very limited. These consents are much more narrow as one interviewee explains,

> Well, it would be narrow. We are not asking, “oh give me your materials so we can do anything.” We only ask to look at one specific question (Interview 1009).

General tendencies are 1) tiered consent for research with specific goals, 2) broad consent for whole genome sequencing, 3) narrow consent for research involving diagnostic tests or specific diseases, and 4) a different protocol based on the study (Fig 3).

Figure 3: The Level of Consent Used



Genomic scientists and clinicians use different types and approaches of informed consent for similar practices with no apparent standardization or clear rationale. This is an area where more guidance could be helpful to ensure research participants are adequately informed and protected. Using one type of consent when another is more appropriate does not protect the participant or the researcher or facilitate the most advantageous use of the resultant data.

Language and Length of Consent Forms

We classified active BC genome researchers as either 1) researchers or 2) clinical researchers (clinicians who also conduct research). Many use different types of consent based on the parameters of the study as discussed above. However, it is clear authors of consent forms use text from previous studies, which is then updated for the current study. The length of the forms has increased over the years as new text is added due to new regulations as well as changes in technology. Clinical trial consent forms are even longer as they need to explain toxin and drug interactions and can be over 20 pages long. These are brought home by patients and subsequently discussed with the clinician to ensure a thorough consent process.

Active BC researchers expressed the need to create shorter forms with suitable language for the average research participant. It is paramount to update the length and level of information in consent materials to render participants knowledgeable and in control of their data as much as possible. When consent forms include text regarding whole exome or whole genome sequencing, they can become very technical and complicated. One interviewee reported the process of consenting an individual taking up to eight hours with this type of detailed consent form. This clinician questioned whether the participant needed to know all the details contained in the form. One interviewee further questions these forms,

> I find them very ridiculous because the average person cannot understand any of those consents and even the average scientist if you asked them serial questions about it, they would fail. So how can we expect the average person to understand that (Interview 1009).

Clearly the interviewees feel the length and language of informed consent forms may be a hindrance to participation in research studies. However, interviewees did emphasize this is not a barrier as recruitment statistics are very high. Guidance is required to ensure these forms are

effectively serving the purpose of informed consent to ensure participants understand the research in which they agree to participate.

Consent Process and Content

Review of the literature, policy documents, interview data, and a survey of consent forms reveals very little discussion of the risks associated with study participant and patient genomic information and the Internet. Traditional consent forms assume the investigator controls the data and can discard or return the data to the participant. However, investigators often are required to upload genomic information to public or semi-public DNA databases by journal publishers and granting agencies. At this point, they lose control of the data. Other parties can access the data across the world. For example, individuals consenting to clinical studies should know that their DNA information may be uploaded to a shared/public DNA database. This is an ethical and legal issue for the researcher/clinician/care provider.

Many active BC researchers admit their informed consent forms do not contain language related to the Internet. When asked about uploading data to public repositories (often a requirement of a publishing a study in an academic journal) interviewees clarify data is in fact available through online sources. However, the data is anonymized meaning it does not contain patient identifying information. One researcher explains,

> So by law we're not allowed to- we double blind the patient identity. So the information eventually becomes tagged with metadata from the patient but never with the patient's identity. And so that is encoded with any information that is made available on the Internet. So nobody could ever trace that information back to the person who that information came from (Interview 1015).

Active BC researchers are very clear they anonymize data before research is conducted. However, when asked about the process of relinking participant/patient identification with samples, answers varied widely. Some project leaders possess a spreadsheet of sample IDs which can be linked with sample donors. This appears to be the case in clinical research where the study participants are also patients. However, for basic research or population studies, the project leaders are not given the identifying information. These respondents outlined processes involving medical health officers or other organizational bodies who must be contacted when relinking is necessary. It is clear each organization has a unique process for relinking information. Situations necessitating relinking of data with identifiers included finding a sequence that needed to be reported to the patient's family doctor, a suspicious finding important to public health, and gathering additional data from a participant to be combined with existing data.

Currently, active BC researchers are relying on anonymizing data to protect participants when data is published in online repositories. The current belief is de-linking data is sufficient in protecting the participant. This may be true, yet the potential for re-identification must be clearly explained to effectively protect both researcher and participant in case future technologies allow easier identification of participants. One interviewee ponders,

> The whole field is so new that...these huge data clouds are starting to generate around each individual. How that all plays out I have no idea (Interview 1012).

However, releasing data is imperative for the progress of science as one interviewee comments about the ethics of this issue,

> So in a sense that's implicit in ethics, right, where you want to make the data about the patient freely available, but the data on the patient should be completely private (Interview 1015).

Genomic data is sensitive because if identified, it contains information about not only the donor, but about his or her family. One clinical researcher noted how results can affect families:

> So we've had circumstances in families that carry dominant genetic diseases with people who are attested not to carry the disease feel gene excluded. They feel that they're not a part of the family in a way that people who have suffered are. They perceive that they're treated that way (Interview 1026).

Further, once released online, genomic data can be re-analyzed for purposes other than those covered in initial consent. This cannot be controlled once data is released as it is uncontrollable and indestructible. This aspect of genomic research should be outlined in the informed consent process.

Return of Research Results

The issue of returning research results is very different for researchers versus clinical researchers. Being in very different circumstances and with different ethical responsibilities, this finding is not surprising. As genomics is moving into the clinical arena and eventually into the health system, we feel the clinician responses are more relevant when looking toward the future of clinical genomics. Of course, research will continue to inform clinical genomics (for example, by finding new disease links to genomic mutations) but the responsibility of the researcher is very different from that of the clinician.

We found three main reasons for returning *clinical* research results. First, if the result can change treatment for the patient it is imperative to communicate this result. This might include the identification of a potentially beneficial experimental treatment or alternatively excluding a patient from a particular therapy based on genomic profiling, so this result would have to describe in detail for the patient to understand any follow-up therapy decisions. One clinical researcher explains,

> And if I'm going to make a decision based on something that's experimental, genomic profiling, then I need [the patient] to understand how experimental it is. And so we go through that in detail (Interview 1024).

Second, if the result is part of the clinical question then it would naturally be returned. One clinical researcher simply states,

> We always return the results that are related to the clinical question. That's the deal that we have with the families (Interview 1026).

Third, many clinicians indicated patients often ask for results and they are either required to (by funder or consent agreements) or desire to fulfill the request. Some very knowledgeable patients ask for specific information, especially those with rare diseases who have become advocates for themselves. Some patients appreciate the cutting-edge nature of the genomic technologies of these studies and find the results help in making treatment decisions. The detail of the result given depends on the patient as described by one clinical researcher,

> So there's some patients who want to go through all the different permutations and there are some that just don't have that level of sophistication and they just want to know the basics of what we came up with so we have a meeting about the results (Interview 1024).

We found two main reasons for not *currently* returning clinical research results held by clinicians. First, there is no consensus on how or what to return. Many clinicians expressed the desire for a standard, quality controlled system for returning results. These results must be verified and validated in the same manner as clinical tests. This issue is clearly under discussion as explained by one clinical researcher:

> So there's not one consensus on how data should be explained or discussed with a patient or how much or what to do with germline mutations and all that. So it's an ongoing discussion and we have a lot of discussion about it (Interview 1024).

Second, there is a fear of patients misunderstanding the results. Additional resources (such as genetic counselors) are needed for this downstream process which is not yet in place. This stems from not having a proper procedure in the healthcare system for handling these type of results.

Researchers have two unique reasons for not returning *research* results. It must be emphasized that the following reflect the experiences of researchers working outside the clinical environment. The responsibility to the participant is very different as each is viewed as a research sample, and not a patient. First, returning results in the research context may not be appropriate or ethically approved. One interviewee stated,

> I mean again in the research arena that's just a well-known taboo (Interview 1016).

Second, research results are not validated (to a clinical standard) or may be irrelevant to the participant (interesting to researcher but not related to health outcome of participant). Further, the nature of research is that the importance of a result is unknown—that is why it is being researched. One researcher states,

> The concerns about when we do the research concept is that the results aren't validated and we may not know the importance of any particular result (Interview 1023).

Of course, as technology and research evolves, these findings may be validated and become part of clinical tests used by clinicians.

The broad categories for returning or not returning results are summarized in the following figures (Fig 4 and Fig 5).

Figure 4: Reasons for Returning Research Results

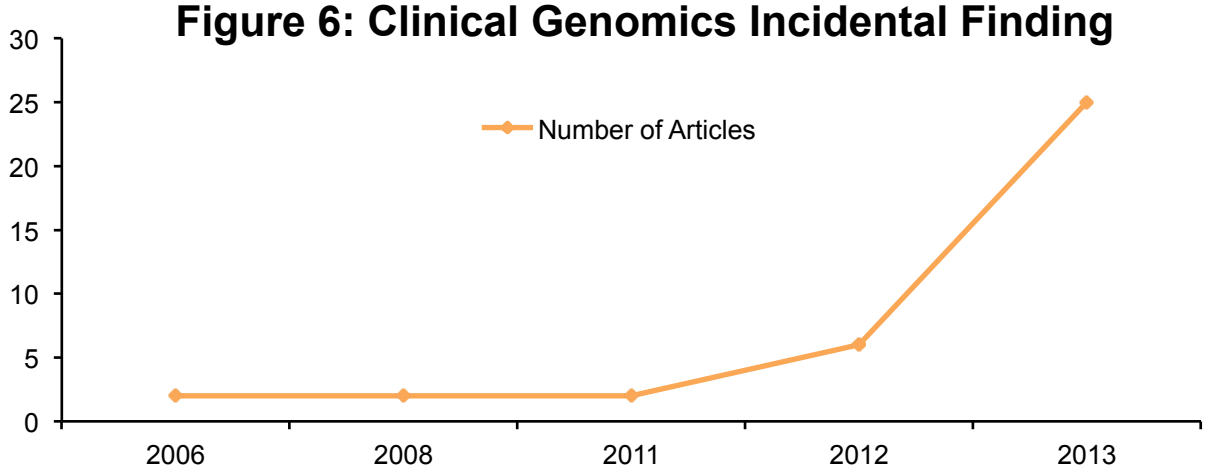
Clinical researchers want to return results (when appropriate) yet a lack of consensus on what and how to return results continues in British Columbia. We feel it is important to stress the difference between the positions held by clinicians and researchers. The future of clinical genomics will be in the hands of clinicians who clearly want guidance and an established system for returning results.

Figure 5: Reasons for not Returning Research Results

Incidental Findings

Genomic incidental findings (GIFs) have become the most pressing issue where clinicians and researchers are uncertain of best practices. Publications regarding this issue have surged in recent years indicating the interest in this topic. Our data confirmed the importance of GIFs as active BC researchers were eager to express their desire for guidance in this area.

Figure 6: Clinical Genomics Incidental Finding



Most researchers claim they are not looking for incidental findings. They are using the data to answer questions and therefore not fishing for other mutations. Further, this type of searching is not covered by most consent forms and funding is not available for those types of analyses. Others view everything as incidental as it is not known what effect every mutation has on the disease state of the individual. One interviewee states,

> …nothing is really incidental right...in the long-run it's all going to be meaningful. It's just a matter of figuring out what the meaning is (Interview 1015).

It again was emphasized that returning incidental findings would require a standard system and consensus of what to return. One clinical researcher notes:

> Well again, if there's a pipeline in place then yes we should. It's my opinion that we should. But that has to be done in an ethically sustainable manner. It has to be done...it's not up to me to decide, it's up to the team to decide. There has to be policy put into place for these types of things (Interview 1010).

Most interviewees were aware of the ACMG guidelines and that there is not something similar in Canada. Our data suggests most clinicians in the position to return these types of findings are eager to return results but need proper guidance. One researcher (working closely with clinicians) comments,

> So I think that very rapidly if we were to look at incidental findings to the same time we would probably adopt the recommendations of certain government agencies. Hopefully those in Canada would have recommendations and failing that probably a professional authority from the US (Interview 1023).

The concept of "incidental finding" may have stretched and may not work for genome findings. Clearly, discussions must continue but further issues other than just what to return are essential. These include pile-on effects of returning GIFs such as effects on patients as well as the healthcare system. Fear exists that both lack of knowledge and resources make returning GIFs very stressful for both clinicians and patients. Therefore, the upstream process of deciding what and how to return results is crucial as described by our interviewees. The outstanding downstream process of incorporating the results into healthcare and patients' lives were not discussed but are present in the literature.

The issue for researchers is different. One researcher explained how the burden on research to look for incidental findings in the research context would be overwhelming. This would essentially turn every research laboratory into a 23andMe type enterprise. It should be clarified that the ACMG guidelines are for clinical laboratories and not research laboratories. Therefore, researchers will likely be able to continue their work and not be responsible for investigating incidental findings in their genomic data samples.

Governance

We interviewed seven individuals involved in policy making and regulation. Our data revealed British Columbia uses a patchwork of regulations and updates individual laws and policies as new technology emerges. Therefore, policy naturally is always lagging behind technology. Interviewees felt that existing policies may be able to be updated to deal with bringing genomics into healthcare. One interviewee states,

> We are in the state where they have very piecemeal statutes that deal with one technology at a time or one problem at a time like GINA. We already have comprehensive privacy law, comprehensive human right law. There might be a way to fit this into our current framework so that we don't need to install something new (Interview 1030).

However, discussions still continue regarding the nature of genomic data and if it can be classified in the same category as personal health information. New risks need to be identified and policies put in place to protect individuals. This individual explained,

> I think genetics information and genomics are one of those areas where people want to use that information for great reason. At the same time, it introduces a lot of new risk we haven't seen before (Interview 1030).

Canada does not have a Genetic Information Nondiscrimination Law like the United States, but it has come up in discussions with policy-makers. This interviewee commented,

> So that prohibited uses model is something we are thinking about as opposed to relying on informed consent at the time of collection. So we are looking at things what are those prohibited use (Interview 1030).

In the policy arena, there is still a line between research and the clinic because they are legislated under two different frameworks. One respondent explained,

> Consent is actually a big part of the discussion because when you look at the health sector, you have public bodies that are under FIPPA, which is not consent-based so that's the health authority. You then have the clinicians who provide the services who are under the Personal Information Protection Act which is consent based. So legislatively, we've got two different frameworks that are in place (Interview 1032).

A further complication is the evolving nature of privacy and security. New technologies are emerging, but at the same time concepts of privacy and security are also changing. As one respondent explained,

> So in law, what you're going to have is something broad that talks about what is reasonable and then you're going to have your policy that is going to be a living document that

> will articulate what is reasonable at this point in time. The policy becomes a living document that is updated as the science is updated. So what is reasonable will be different. And also, what is considered privacy is changing (Interview 1032).

Our data found that genomics is being discussed in the policy arena and that many issues are known and being considered. However, the policy structure in British Columbia uses fragmented laws as each is developed as needed. It is unclear at this point if genomics requires new policy framework or if existing policies can be updated and expanded. Clearly, more work will be done in this area as genomics moves into healthcare and policies are needed to handle the transition.

We focused on the three main areas of informed consent, return of research results, incidental findings, and governance in our analysis. From this analysis and consultation with the literature we have made recommendations for each of these areas. These recommendations are outlined in the next section.

Recommendations

As detailed above, we identified several issues in the areas of informed consent, returning results and genomic incidental findings. The recommendations of our working group are a synthesis of already existing guidelines and novel findings from our project. In essence, the following recommendations are the combination of our document analysis and a three-year research project in which we consulted various stakeholder groups for their input. Together, we join novel insights with existing guidelines.

Principle: Informed Consent

It has been revealed that the types and approaches to informed consent need to be addressed in order to realize the potential for diagnostic tests of specific diseases. The following recommendations are built around the premise of advancing the fundamental principle of informed consent into the clinical context for which it is currently not fit (PHG, 2011; Henderson, 2011).

Recommendation 1: Design a proactive consent process that addresses risks and benefits of digital genomic information

1.1 Emphasize the unique nature of genomic information and the Internet: participant and patient documents such as consent forms and education manuals should include information and language about the potential digital pathways of their genomic information and the associated informational risks. Language should make it clear that clinical genomics generates digital information, which differs from a traditional understanding of the biological specimens and can impact issues of privacy and intellectual property. Similar to already existing guidelines, we recommend informing and educating patients about any potential risks coming from the digital nature of their information (PCSB, 2012; PCSB, 2013).

1.2 Respect the right not to know and patient preferences: Convey the scope of potential incidental findings and engage in shared decision-making process with patient about what types of results may be returned. Refer to the recommended decision matrix and stakeholder decision group. Acknowledge the potential to generate GIFs and the possibility of discovering findings that are presently unknown. Improving the process of informing patients will enable them to better understand the possible discoveries of incidental findings and to decide if they do want to receive those results (PCSB, 2012; PCSB, 2013). This point has been highly contested, especially since the ACMG guidelines from 2013 originally recommended returning *all* results, which indirectly undermines a patient's autonomy not to know. ACMG recently updated this recommendation to include an option to opt-out (ACMG, 2014).

1.3 Contain language/disclaimer that privacy is not absolute: Provide details of data release and sharing, including potential public databases where data could be disseminated. Explain the potential of re-identification of anonymized data. Emphasize the digital nature of clinical genomic data and how this could impact issues of privacy and intellectual property. Current guidelines acknowledge the dichotomy of the intellectual endeavour of genomic medicine which has to respect autonomy and privacy (PCSB, 2012; PCSB, 2013). We recommend making these tensions palpable for patients of genomic tests through appropriate language in the consent forms.

1.4 Describe the data management procedure and the potential for future third party use, such as by researchers or clinicians. This should include where and for how long both biological and digital samples will be stored.

There is a national push to cluster and network genomic technologies (see PHG, 2011), which should be reflected in consent documents.

1.5 Highlight that withdrawing patient/participant data is limited and that the participants *cannot* always withdraw. Explain that digital data is potentially indestructible, especially once it is disseminated in public databases and subsequently used by third parties. While it is generally recommended that participants have the ability to withdraw from clinical research (PHG, 2011), we caution that this might not always be possible due to the networked nature of digital genomic data.

1.6 Explain the social network nature of genomic information and explain the implications of familial issues, such as the return of test results to families of deceased, the disclosure of results to 'at risk family members' and/or other relevant parties, as well as the possibility of needs of family overriding objections of patients/participants. Similar to other guidelines for handling the implications for family members (see Sénécal et al, 2013), we recommend educating patients on the impacts for family members.

Principle: Returning Results

Clinicians and practitioners have a high need for guidance in what genomic information to return in order to deliver quality-controlled results to patients and participants (if appropriate). There is currently no consensus on how or what to return.

Recommendation 2: Return Results and Select Incidental Findings

Results that have scientific validity and clinical utility should be returned in clinical research and point of care settings. This is in line with past studies (see RMGA, 2013; ACMG, 2013) and includes genomic incidental findings as discussed below. While the ACMG guidelines initially recommended that patients are indirectly obliged to accept all the feedback of incidental findings and opportunistic screening (Burke et al., 2013), we recommend that to achieve a high degree of patient autonomy that including the right not to know or to opt-out from certain results is essential. ACMG recently updated its recommendation to allow patients to opt-out of results at the time of sample submission (ACMG, 2014). Complex protocols will have to be established to guide clinical decision-making processes based on accurate and clinically useful results if incidental findings are to become clinically useful (see Friedman, 2013).

Principle: Genomic Incidental Findings

When this type of genomic testing moves into the care setting, doctors are obligated to address any incidental findings in the genomic profile for clinical relevancy (see ACMG, 2013). Therefore, it is important to establish frameworks that acknowledge the ethical regime of an applied health care setting. In this context, we strongly recommend starting with the 2013 ACMG guidelines and recommend that something similar should be put in place in British Columbia and Canada.

Recommendation 3: Develop a 'green, yellow and red light' decision-making matrix

3.1 We recommend a group forms in British Columbia that consists of clinicians, clinical researchers, and genome scientists to decide on a decision-making matrix for managing the re-

turn of genomic incidental findings. This group could potentially consult key stakeholders including care providers, patient advocacy groups, genetic counselors and policy makers[7].

3.2 This group would formulate a management plan for return of research results. Their responsibilities would include: 1) develop a return of results decision matrix; 2) decide which GIFs, if any, will be returned; 3) draft an approach that: a) consults existing guidelines and "criteria for disclosure", b) provides researchers and clinicians with a schematic that is doable, and c) addresses logistical considerations.

The matrix should consist of three classes of findings. 'Green' class findings have both scientific/clinical validity and clinical utility and should be returned. 'Yellow' class findings may have scientific/clinical utility but no consensus on clinical utility. These would be returned at the discretion of the clinical researcher or medical practitioner. 'Red' class findings do not have either scientific/clinical validity or clinical utility and should not be returned.

3.3 The information in the decision-making matrix should be made widely available to clinician, practitioners and researchers. Dissemination methods would include Internet resources such as a web page, social media, and mobile applications. For example, we envision that Twitter could be used for real-time updates and a mobile device app similar to 'Epocrates' could display and visualize most current classes of incidental findings.

Recommendation 4: Revise the Decision Making Matrix on an Annual Basis

We recommend revising the decision-making matrix every year due to the current rate of knowledge discovery and clinical validity. This is widely supported in the clinical community (see ACMG, 2013). Some 'red' findings may move up to yellow or green status and some yellow findings may move up to green status. However, as the rate of discovery progresses presumably at an increasing rate, this revision schedule may need to be altered to ensure new discoveries and most current scientific consensus are reflected in the matrix.

Principle: Governance

Laws and policies in Canada provide patchwork coverage of genomic privacy and data management issues. Our data revealed differing views of whether new laws/policies are required. On further questioning, it became clear there is a disconnect between what interviewees think exists versus what is actually enforced in Canada. Most agreed current laws do not specifically cover genomics but not all saw this as an issue. Knowledge was clearly driven by institutions (eg: local REB or funder policies) and use was practical rather than ethical (such as following tri-council guidelines to satisfy funder requirements). Our data shows that policy experts consider that the current health care policies are not up to task to handle the new type of genomic information in the context of British Columbia health care setting.

Recommendation 5: Address the Policy Patchwork in British Columbia

We recommend a multi-stakeholder network be created in British Columbia to address the limitations of current healthcare and privacy policies, as well as the potential need for new health information and data guidelines. This network would consist of key stakeholders including care

[7] In British Columbia, these stakeholder organizations could include PHSA, TFRI, MSFHR, GSC, BCCA, VGH, BC Children's Hospital, universities, GBC, and OIPC, for example.

providers, patient advocacy groups, genetic counselors, policy makers and organizations such as PHSA, TFRI, MSFHR, GSC, BCCA, VGH, BC Children's Hospital, universities, GBC, and OIPC, for example.

Appendix 1: Tables and Figures

Figure 7: 'The Wheel of Issues'

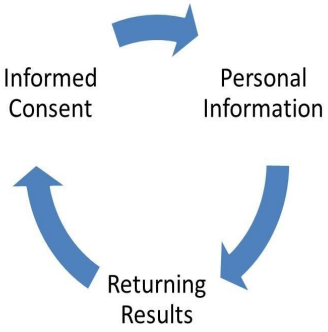


Figure 8: Clinical Genomics Incidental Findings

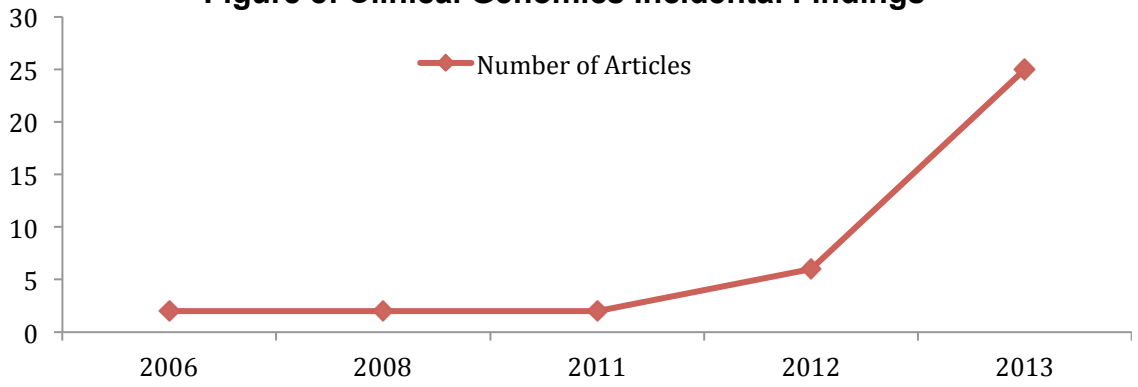


Figure 9: Genomic Return Research Results

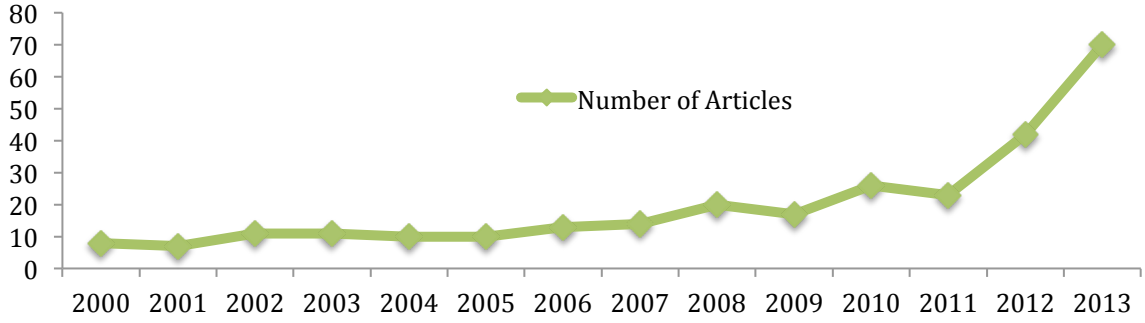


Figure 9: Clinical Genomics Return Research Results

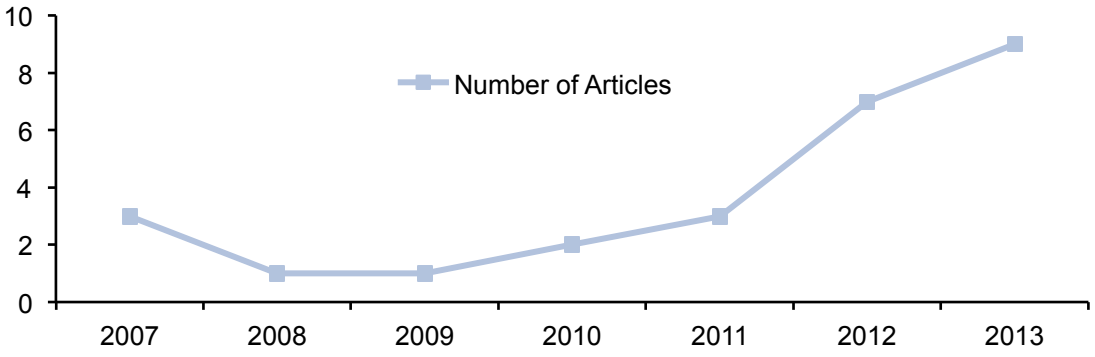


Figure 10: Clinical Genomics Informed Consent

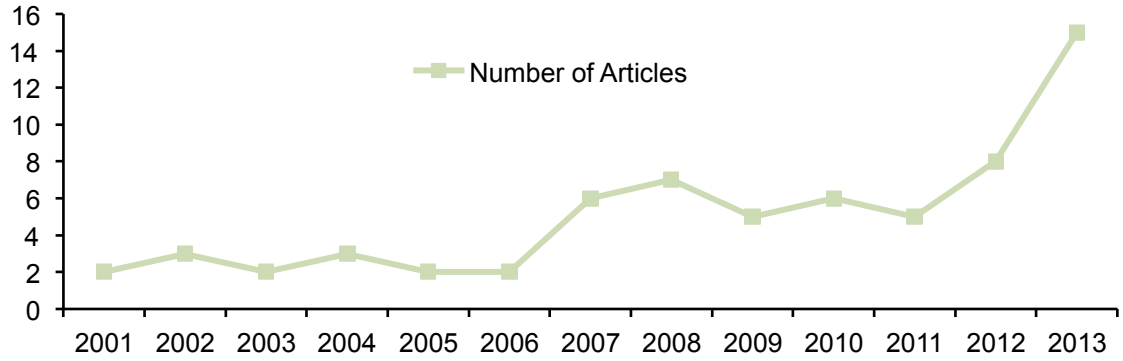
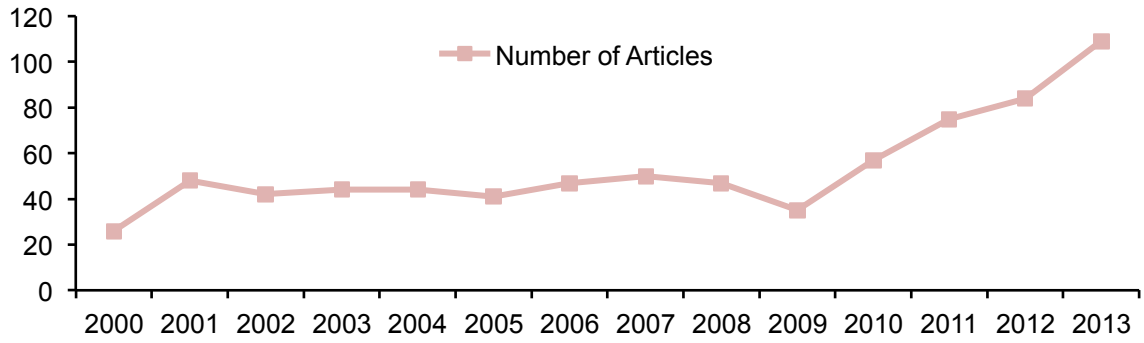


Figure 11: Genomic Informed Consent



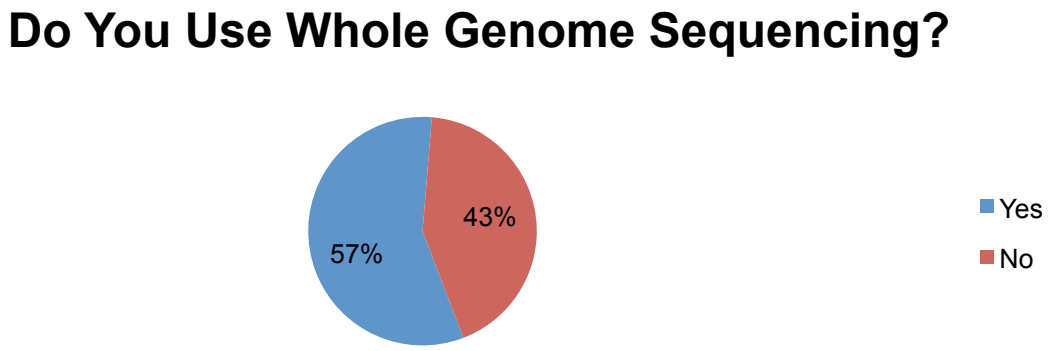
Appendix 2: Abbreviations

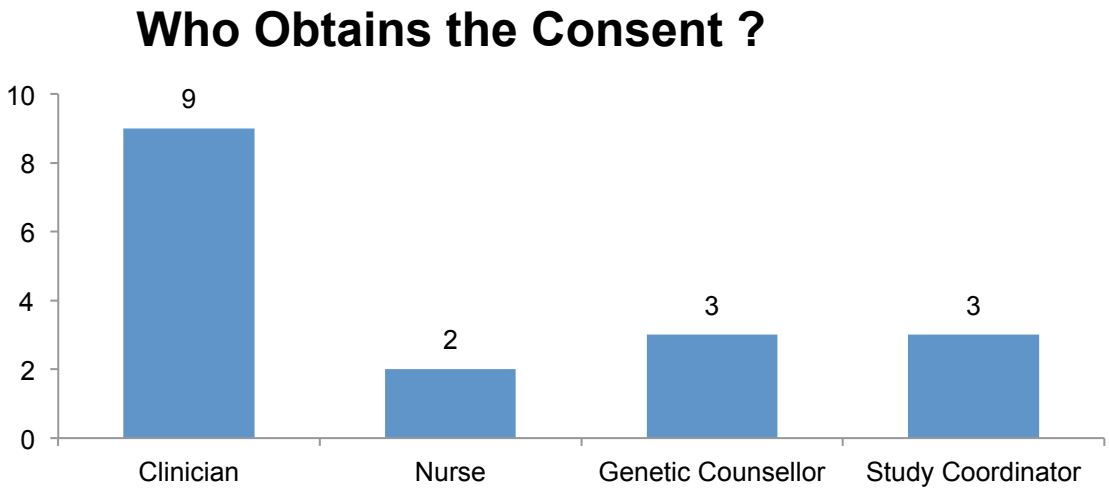
ACCE: American College of Clinical Engineering
ACMG: American College of Medical Genetics
AML: Acute myeloid leukemia
BC: British Columbia
BCCA: BC Cancer Agency
BRCA: breast cancer antigen
CIHR: Canadian Institutes of Health Research
CLIA: Clinical Laboratory Improvement Amendments
DNA: Deoxyribonucleic acid
DTC: Direct to consumer
FOIA: Freedom of Information Act
GBC: Genome BC
GIF: Genomics Incidental Findings
GINA: Genetic Information Nondiscrimination Act
GSC: Genome Sciences Centre
GWAS: Genome-wide Association Study
HUGO: Human Genome Organization
ICGC: International Cancer Genome Consortium
MSFHR: Michael Smith Foundation for Health Research
NIH: National Institutes of Health
NSERC: Natural Sciences and Engineering Research Council
OIPC: Office of the Information and Privacy Commissioner
PCSBI: Presidential Commission for the Study of Bioethical Issues
PEM: Patient Education Material
PHG: Public Health Genetics
PHSA: Provincial Health Services Authority
PIPEDA: Personal Information Protection and Electronic Documents Act
UBC: University of British Columbia
REB: Research Ethics Board
RMGA: Network of Applied Genetic Medicine
SAC: Scientific Advisory Committee
SNP: Single-nucleotide polymorphism
SSHRC: Social Sciences and Humanities Research Council
TCPS2: 2nd edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans
TFRI: Terry Fox Research Institute
WGS: Whole Genome Sequencing
VGH: Vancouver General Hospital

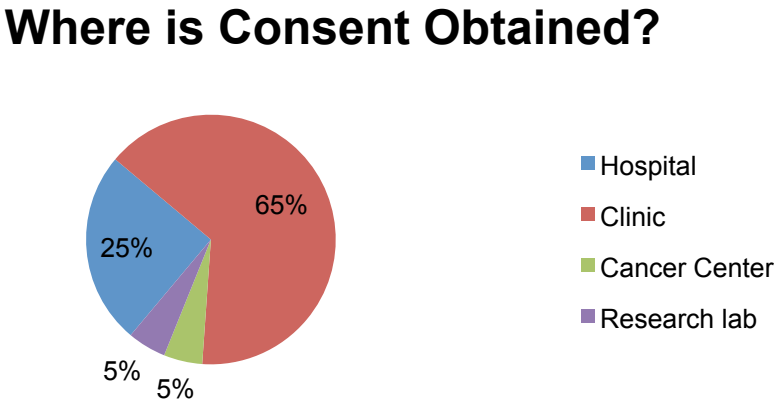
Appendix 3: List of Interviewees

Code	Interview Date	Category
1000	11-Dec-12	Clinical Researcher
1001	14-Jan-13	Clinical Researcher
1002	23-Jan-13	Clinical Researcher
1003	3-Feb-13	Clinical Researcher
1004	5-Feb-13	Researcher
1005	15-Feb-13	Researcher
1007	18-Feb-13	Researcher
1006	18-Feb-13	Clinical Researcher
1008	19-Feb-13	Clinical Researcher
1009	8-Mar-13	Clinical Researcher
1010	8-Mar-13	Clinical Researcher
1011	15-Mar-13	Researcher
1012	19-Mar-13	Researcher
1013	25-Mar-13	Researcher
1014	25-Mar-13	Clinical Researcher
1015	2-Apr-13	Researcher
1016	3-Apr-13	Researcher
1017	29-May-13	Researcher
1018	3-Jun-13	Researcher
1019	17-Jun-13	Researcher
1020	18-Jun-13	Clinical Researcher
1021	19-Jun-13	Researcher
1022	26-Jun-13	Researcher
1023	28-Jun-13	Researcher
1024	4-Jul-13	Clinical Researcher
1025	8-Jul-13	Researcher
1026	9-Jul-13	Clinical Researcher
1027	17-Jul-13	Researcher
1028	19-Jul-13	Researcher
1029	7-Oct-13	Clinical Researcher
1030	6-Nov-13	Policy Official
1031	25-Nov-13	Policy Official
1034	28-Nov-13	Policy Official
1032	28-Nov-13	Policy Official
1033	28-Nov-13	Policy Official
1034	29-Nov-13	Policy Official
1035	29-Nov-13	Policy Official

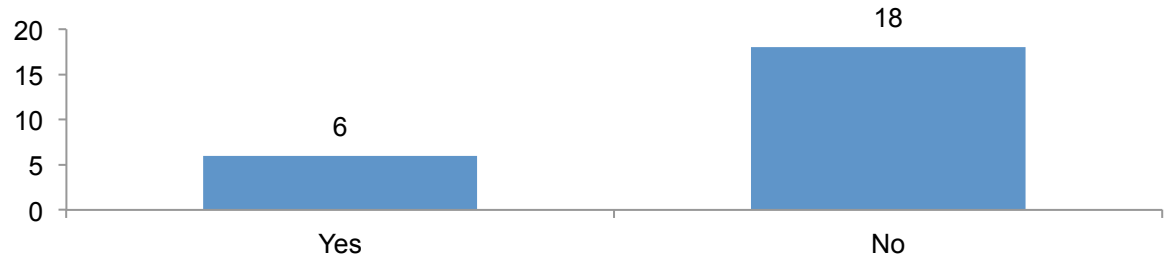
Appendix 4: Quantitative Interview Data





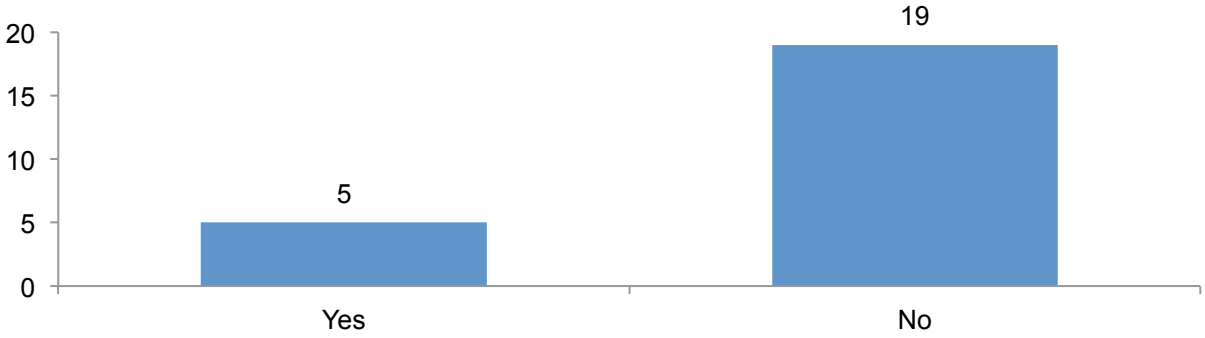


Do You Provide Patient Education Materials?



Patient Knowledge About Genomics

Do You Involve Genetic Counselors?



References

ACMG (2013). *ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing Report***.** Retrieved May 4, 2013 from http://www.acmg.net/docs/ACMG_Releases_Highly-Anticipated_Recommendations_on_Incidental_Findings_in_Clinical_Exome_and_Genome_Sequencing.pdf

ACMG (2014). ACMG Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results. Retrieved May 7, 2014 from https://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf

Baars MJ, Henneman L, Ten Kate LP. (2005). Deficiency of knowledge of genetics and genetic tests among general practitioners, gynecologists, and pediatricians: a global problem. *Genet Med., 7*(9):605-10.

Barr G. (2010). Staking the Public Trust on Newborn Dried Blood Spot Retention. Health Law Rev.; 18: 30–38.

Bathe, O. F., & McGuire, A. L. (2009). The ethical use of existing samples for genome research. *Genetics in Medicine : Official Journal of the American College of Medical Genetics, 11*(10), 712-715.

Belmont Report (1979). *The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research*. Retrieved May 4, 2013, from http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

Black, L., Avard, D., Zawati, M.H., Knoppers, B.M., Hébert, J., Sauvageau, G. & Leucegene Project. (2013). Funding considerations for the disclosure of genetic incidental findings in biobank research. *Clin Genet., 84*(5):397-406.

Black, L., & McClellan, K. A. (2011). Familial communication of research results: A need to know? *The Journal of Law, Medicine & Ethics : A Journal of the American Society of Law, Medicine & Ethics, 39*(4), 605-613.

Boddington, P. (2010). Relative responsibilities: Is there an obligation to discuss genomics research participation with family members? *Public Health Genomics, 13*(7-8), 504-513.

Borzekowski, D. L., Guan, Y., Smith, K. C., Erby, L. H., & Roter, D. L. (2013). The Angelina effect: immediate reach, grasp, and impact of going public.*Genetics in Medicine*.

Burke, Wylie, Armand H. Matheny Antommaria, Robin Bennett, Jeffrey Botkin, Ellen Wright Clayton, Gail E. Henderson, Ingrid A. Holm, et al. (2013) "Recommendations for Returning Genomic Incidental Findings? We Need to Talk!" *Genetics in Medicine* 15(11): 854–859.

Bush, W. S., & Moore, J. H. (2012). Chapter 11: Genome-wide association studies. *PLoS Computational Biology, 8*(12), e1002822.

Cheung, C. C., Martin, B. R., & Asa, S. L. (2013). Defining diagnostic tissue in the era of personalized medicine. *Canadian Medical Association Journal, 185*(2), 135-139.

Caulfield, T., & Knoppers, B. M. (2010). *Consent, Privacy & Research Biobanks* (Policy brief No. 1). Genome Canada. Retrieved from http://www.genomecanada.ca/medias/pdf/en/GPS-Policy-Directions-Brief.pdf

Caulfield, T., McGuire, A. L., Cho, M., Buchanan, J. A., Burgess, M. M., Danilczyk, U., Timmons, M. (2008). Research Ethics Recommendations for Whole-Genome Research: Consensus Statement. *PLoS Biology*, *6*(3), e73.

Caulfield, Timothy, Christen Rachul, and Erin Nelson. (2012). "Biobanking, Consent, and Control: A Survey of Albertans on Key Research Ethics Issues." *Biopreservation and Biobanking* 10(5): 433–438.

Clayton, E. W., & McGuire, A. L. (2012). The legal risks of returning results of genomics research. *Genetics in Medicine : Official Journal of the American College of Medical Genetics, 14*(4), 473-477.

Dorschner MO, Amendola LM, Turner EH, Robertson PD, Shirts BH, Gallego CJ, Bennett RL, Jones KL, Tokita MJ, Bennett JT, Kim JH, Rosenthal EA, Kim DS; National Heart, Lung, and Blood Institute Grand Opportunity Exome Sequencing Project, Tabor HK, Bamshad MJ, Motulsky AG, Scott CR, Pritchard CC, Walsh T, Burke W, Raskind WH, Byers P, Hisama FM, Nickerson DA, Jarvik GP. (2013). Actionable, pathogenic incidental findings in 1,000 participants' exomes. *Am J Hum Genet, 93*(4):631-40.

Evans, BJ. (2013). Minimizing liability risks under the ACMG recommendations for reporting incidental findings in clinical exome and genome sequencing. *Genet Med*, *15*(12):915-20.

Fernandez, C. V., Strahlendorf, C., Avard, D., Knoppers, B. M., O/'Connell, C., Bouffet, E., … Sorensen, P. H. (2013). Attitudes of Canadian researchers toward the return to participants of incidental and targeted genomic findings obtained in a pediatric research setting. *Genet Med*, *15*(7), 558–564.

Francke, U., Dijamco, C., Kiefer, A. K., Eriksson, N., Moiseff, B., Tung, J. Y., & Mountain, J. L. (2013). Dealing with the unexpected: consumer responses to direct-access BRCA mutation testing. *PeerJ*, *1*, e8.

Friedman, J. (2013). The UBC Medical Curriculum and the Genomic Revolution. *UBC Medical Journal, 4*(2), 6-7.

Hackett, E.J., Amsterdamska, O., Lynch, M. & Wajcman, J (eds.) (2008) The Handbook of Science and Technology Studies, third edition. Cambridge, MA and London: MIT press, 2007.

Homer, N., Szelinger, S., Redman, M., Duggan, D., Tembe, W., Muehling, J., … Craig, D. W. (2008). Resolving Individuals Contributing Trace Amounts of DNA to Highly Complex Mixtures Using High-Density SNP Genotyping Microarrays. *PLoS Genet*. *4*(8): 1-9.

Henderson, G. E. (2011). Is informed consent broken? *The American Journal of the Medical Sciences, 342*(4), 267-272.

Kamenova, K., Reshef, A., & Caulfield, T. (2013). Angelina Jolie/'s faulty gene: newspaper coverage of a celebrity/'s preventive bilateral mastectomy in Canada, the United States, and the United Kingdom. *Genetics in Medicine*.

Knoppers, B. M., & Dam, A. (2011). Return of Results: Towards a Lexicon? *The Journal of Law, Medicine & Ethics*, *39*(4), 577–582.

Knoppers, B. M., Joly, Y., Simard, J., & Durocher, F. (2006). The emergence of an ethical duty to disclose genetic research results: international perspectives. *European Journal of Human Genetics*, *14*(11), 1170–1178.

Knoppers, B. M., & Laberge, C. (2009). Return of "Accurate" and "Actionable" Results: Yes! *The American Journal of Bioethics*, *9*(6-7), 107–109.

Knoppers, B. M., & Lévesque, E. (2011). Return of Research Results: How Should Research Results Be Handled? *The Journal of Law, Medicine & Ethics*, *39*(4), 574–576.

Kronenthal, C., Delaney, S. K., & Christman, M. F. (2012). Broadening research consent in the era of genome-informed medicine. *Genetics in Medicine : Official Journal of the American College of Medical Genetics, 14*(4), 432-436.

Kvale, S. (2007). *Doing Interviews.* London, England: SAGE Publications, Ltd.

McGuire, A. L., & Beskow, L. M. (2010). Informed consent in genomics and genetic research. *Annual Review of Genomics and Human Genetics, 11*, 361-381. doi: 10.1146/annurev-genom-082509-141711; 10.1146/annurev-genom-082509-141711

McGuire, A. L., Oliver, J. M., Slashinski, M. J., Graves, J. L., Wang, T., Kelly, P. A., Hilsenbeck, S. G. (2011). To share or not to share: A randomized trial of consent for data sharing in genome research. *Genetics in Medicine : Official Journal of the American College of Medical Genetics, 13*(11): 948-955.

McGuire, Amy L., Steven Joffe, Barbara A. Koenig, Barbara B. Biesecker, Laurence B. McCullough, Jennifer S. Blumenthal-Barby, Timothy Caulfield, Sharon F. Terry, and Robert C. Green. (2013). "Ethics and Genomic Incidental Findings." *Science*. 34 6136): 1047–1048.

Middleton, A., Patch, C., Wiggins, J., Barnes, K., Crawford, G., Benjamin, C. & Bruce, A. (2014). Position statement on opportunistic genomic screening from the Association of Genetic Nurses and Counsellors (UK and Ireland). *Eur J Hum Genet*.

Miller, F.A., Hayeems, R.Z., Bytautas, J.P., Bedard, P.L., Ernst, S., Hirte, H., Hotte, S., Oza, A., Razak, A., Welch, S., Winquist, E., Dancey, J. & Siu, L.L. (2013). Testing personalized medicine: patient and physician expectations of next-generation genomic sequencing in late-stage cancer care. *Eur J Hum Genet*.

PHG Foundation (2011). *Next steps in the sequence: The implications of whole genome sequencing for health in the UK***.** Retrieved from http://www.phgfoundation.org/pages/wholegenome.htm

Presidential Commission for the Study of Bioethical Issues (PCSB). (2013). *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research and Direct-to-Consumer Contexts*. Retrieved from http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf

Presidential Commission for the Study of Bioethical Issues (PCSB). (2012). *Privacy and Progress in Whole Genome Sequencing*. Retrieved from http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf http://bioethics.gov/node/3169Secko,

D. M., Preto, N., Niemeyer, S., & Burgess, M. M. (2009). Informed consent in biobank research: A deliberative approach to the debate. *Social Science & Medicine (1982), 68*(4), 781-789.

Sénécal K., Lévesque E., Fernandez C., Tassé A.M., Zawati M.H., Knoppers B.M., Avard D. (2013). *RMGA Statement of Principles on the Return of Research Results and Incidental Findings*.

Taylor, P. (2008). Personal genomes: When consent gets in the way. *Nature, 456*(7218): 32-33.

TCPS2 (2010). *TCPS 2—2nd edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.* Retrieved May 4, 2013 from http://pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/

Wallace, S. E. (2011). The needle in the haystack: International consortia and the return of individual research results. *The Journal of Law, Medicine & Ethics : A Journal of the American Society of Law, Medicine & Ethics, 39*(4): 631-639.

Wolf, S. M., Crock, B. N., Van Ness, B., Lawrenz, F., Kahn, J. P., Beskow, L. M., et al. (2012). Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genetics in Medicine*, *14*(4), 361–384.

Wolf, S. M. (2013). Return of Individual Research Results and Incidental Findings: Facing the Challenges of Translational Science. *Annual Review of Genomics and Human Genetics.* 14(1): 557–577.

Zawati M.H., Knoppers B.M. (2012). International normative perspectives on the return of individual research results and incidental findings in genomic biobanks. *Genet Med, 14*(4):484-9.