

Helping Clinicians Identify the Clinical Utility of Genetic Tests

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Abstract

Objectives: Medical genetics presents great potential for improving healthcare outcomes, but faces challenges for managing the test results. This paper focuses on the gaps in clinician knowledge regarding genetic testing and asks what health information technologies (IT) can help non-specialists (e.g., General Practitioners) to identify the utility of an available genetic test. **Methods:** This is part of a grounded theory study in the context of New Zealand genetic services to identify core issues in genetic information management. 48 genetic service stakeholders were interviewed and their comments triangulated with our notes and organizational documents or guiding policies in the domain. **Results:** Little information is available to clinicians regarding 1) clear evidence for test utilities, 2) protocols for choosing among service models, and 3) clinical guidelines for patient management based on test results. It appears that these uncertainties are related to the ambiguity in clinician attitudes towards referring a patient for a test and in acting on the test results. **Discussion:** The heavy dependence on clinician knowledge presents opportunities for health IT innovators to assist clinicians in key tasks, such as assessing disease risks, identifying the benefits and availability of genetic tests, streamlining referral processes, and managing patients according to test results. **Conclusions:** The gaps in clinician knowledge regarding genetic testing, especially regarding its clinical utility, are a barrier for involving healthcare providers in genetic services delivery. Decision support systems and electronic referral systems may empower healthcare professionals with knowledge and tools to improve utilization of genetic information for better healthcare outcomes.

Keywords: Decision Support Systems; Clinical; Genetic Services; Genetic Testing; Information Technology

1 Introduction

Recent development in human genetics science and biomedical research has vastly increased our understanding on the genetic component of human diseases, especially since the completion of the human genome sequencing in 2003 [1]. More and more associations are identified between genetic variations and conditions. Genetic test results, along with the information gained from family history and physical examination, are used in clinical practice to assist diagnosis, prognosis, and personalized treatment. Given the sensitive nature of medical genetic data, challenges emerge for managing

genetic test results in the healthcare system. This report is part of a grounded theory study to identify core issues in genetic information management. Our journey to wider use of genetic information starts with this first step of helping clinicians identify the clinical utility of genetic tests.

Genetic testing is a complex technology and it has limitations. Not all tests are evaluated for their clinical validity and utility. The clinical utility of a genetic test is defined as the likelihood that the test will lead to an improved health outcome [2]. Genetic test utilities refer to a more encompassing concept of net benefit; and the sources of its social utility involve psychosocial,

ethical, legal, and social issues that contribute to the net balance between benefits and harms for tested individuals, their families, and the population at large [3]. Moreover, heterogeneity, prevalence, and penetrance (which is a measure of the proportion of genetically similar individuals that show any phenotypic manifestation of a mutation that they have in common [4]) of a genetic test also influence its clinical validity (sensitivity, specificity, and predictive value) and utility [5]. With these complexities, gaps have been reported in clinician knowledge regarding genetic testing, possibly relevant to the uncertain utility of genetic tests. This paper focuses on understanding the nature of such gaps in New Zealand genetic services delivery system and identifies opportunities in health information technologies (IT) development that may help in bridging the gaps.

A 2003 national survey in New Zealand reported a gap in General Practitioners' (GPs') knowledge on genetics, and the appropriate terminology and procedures in three case scenarios – breast cancer, cystic fibrosis and Huntington disease [6, 7]. In this context, we address the need to help clinicians identify useful genetic tests and ask: How do the mixed perceptions on clinical utility of genetic tests influence the uptake of medical genetic testing in clinical practice? Do healthcare providers such as GPs know when to use a genetic test and where to get it? What health information technologies (IT) can help non-specialists (e.g., GPs) to identify the utility of an available genetic test? In an earlier paper [8], we reported that New Zealand clinicians, including GPs, medical specialists, midwives, nurses, and other community-based health practitioners, are supported by a formal genetic service program. This program consists of two regional offices – the Northern Regional Genetic Service and the Central and Southern Regional Genetics Service. Clinical geneticists and genetic counsellors in these offices provide genetic services through a Patient-Doctor-Counsellor model or a Patient-Counsellor-Lab Model. In addition, two more genetic services delivery models are operating in the country, i.e. Patient-Doctor-Lab Model and Patient-Lab (Commercial) Model. In the context of these multiple pathways to genetic testing, this paper identifies the challenge to help non-specialists (e.g., GPs) act on opportunities where genetic tests are useful and discusses the opportunities for health IT innovators to support the services delivery system.

2 Methods

This study was conducted in the context of New Zealand genetic services, using the grounded theory approach

described by Charmaz [9]. The research aimed at addressing challenges specific to medical genetic testing and associated clinical care. Stakeholders of genetic services were interviewed about their experiences in using genetic tests for healthcare purposes, and their opinions about challenges in clinical genetic information management. A semi-structured interview protocol was developed for gaining ethics approval (which was granted) and was adjusted as the interviews progressed. Questions were used to prompt participants to talk about topics, concepts, themes, and issues that they felt were essential to the research. These questions include “What do you think would be the appropriate means of distribution for genetic testing results?” “What changes would you like to see in handling and managing genetic information?” and “What are the current and potential challenges from your point of view?”

Convenience sampling was used to start collecting interviews with patients, doctors, genetic counsellors, and genetic testing laboratory scientists. Snowballing then occurred when we asked interviewees for suggestions about whom to include in the study. Additional data were iteratively gathered using the principle of theoretical sampling until the researcher began to see the emergence of an appropriate theory [10]. While the theory of “unleashing the power of human genetic variation knowledge” (reported at [11] as our final result of this PhD research) was emerging, we used theoretical sampling to gain insights from particular groups of stakeholders, e.g., medical specialists, patients, and health insurance providers. A total of 48 participants was interviewed. They fall into nine categories according to their roles and characteristics: patients and family members (numbering 8), healthcare providers (8), regional genetic services providers (11), genetic testing laboratory scientists (3), governance (3), health IT professionals (4), researchers (5), directors of a health institution that provides genetic services (7), and clinical advisors at an indirect health service (5). Some participants have more than one role in the system, for instance as both clinician and director.

The interviews were transcribed. The interview transcripts were processed by multiple coding (line-by-line open coding in QSR NVIVO software [12], axial coding, and selective coding) and constant comparative analysis, as suggested by Strauss and Corbin [13]. Data analysis was conducted as interviews proceeded until we reached data saturation. As recommended by Caelli, Ray and Mill [14], the participant comments are triangulated with our field notes (e.g. observation of what actually is practiced) and a review of organizational documents and guiding policies in the domain, such as best practice guidelines by the Human Genetics Society of Australia-

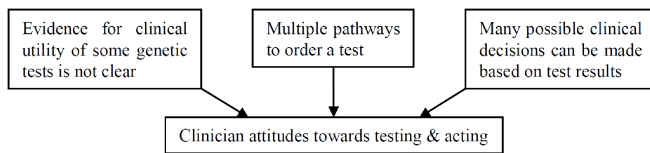


Figure 1: Clinical utility factors on clinician attitudes towards medical genetic testing.

sia (HGSA) [15] and New Zealand Health Privacy Code of Practice [16]. The themes that emerged from the analysis of multiple perspectives concern how the genetic services system should work, why genetic data sharing is inhibited, and what the barriers are for wider use of genetic information. Validation of the identified themes was achieved by triangulation with observation and documents, as well as by confirmation from more participants on the subjects in further interviews. One topic that appeared to be emphasised as it emerged in the NVIVO database is about the uncertain clinical utility of genetic tests and the associated gaps in clinician knowledge regarding the usefulness, referral procedures, and consequences of genetic testing.

3 Results

Findings based on the interviews revealed a set of concerns that are perceived as impediments for using genetic information to improve healthcare outcomes. One major barrier for involving healthcare providers in genetic services delivery is related to the clinicians' mixed perceptions on clinical utility of genetic tests. Participant comments highlighted the scarcity of information that is available to clinicians regarding 1) clear evidence for test utilities, 2) agreed protocols for choosing among multiple test pathways, and 3) clinical guidelines for deciding between many possible patient management actions based on test results. It appears that with these uncertainties there is some ambiguity in clinician attitudes towards using medical genetic tests and acting on the test results, as shown in Figure 1.

3.1 We need clear evidence proving it's useful!

Genetic testing is perceived by our participants as a complex technology. A GP refers to it as a "complex issue," between themes for predicting disease susceptibility and with the potential for harm. It is common that a genetic test cannot locate any abnormality. Such results often cannot confirm or exclude a genetic condition. Moreover, some genetic test results may offer only limited information for clinical use. For example, a Huntington's disease mutation may tell nothing about how the disease will affect an individual, and only tell

very vaguely about the age at which it may affect that individual. Alternatively, the uncertainty can be attributed to the limitation of current genetics knowledge. As a genetic testing laboratory director explained: "Labs find a lot of mutations. And it's difficult to know whether they're causing disease or whether they're just there. ... The current knowledge of variants is incomplete." It also appeared that the inadequate information on test prevalence, penetrance, and risk assessment protocols is a concern for clinicians. A GP related: "Genetic information would perhaps apply more specifically to genetic markers, and we might want to see a few more instances before a clearer picture emerges." In order to involve clinicians in the genetic services delivery system, clear evidence on test utility has to be available to them, as mentioned by a GP: "Until we have much clearer information about risk and prognosis, primary care is not likely to be significantly involved, and will likely remain in the specialist sphere for the foreseeable future anyway."

3.2 Multiple pathways to get a genetic test done?

Some genetic tests, such as presymptomatic tests for untreatable diseases, are handled sensitively with proper pre- and post- test counselling. Other tests, such as carrier status tests for serious conditions, can also result in a need for careful counselling on issues such as family planning. Regional genetic services prefer these tests go through their formal program because of the advantages of involving a genetic counsellor – what we have previously dubbed the Patient-Doctor-Counsellor model and the Patient-Counsellor-Lab Model. For example, they have informed consent procedures in place, they provide adequate counselling, and maintain a family folder. However, these two models have limitations such as workforce shortage in regional genetic services and weaknesses such as poor communication with healthcare providers. As a result, there are two more models operating in the country: the Patient-Doctor-Lab Model (direct genetic test ordering within the doctor-patient relationship) and Patient-Lab (Commercial) Model (a patient liaising directly with a commercial lab). We found that genetic testing laboratories receive a large number of test requests directly from primary and secondary healthcare providers (i.e., Patient-Doctor-Lab Model). Laboratory personnel believe that these clinicians know what they want, but sometimes need help interpreting the results, and sometimes fall down a bit on the subtle ethical issues, e.g., not obtaining informed consent before testing (as they haven't explained to the patient what the result could be and what that could

mean). Concerns are also raised regarding the knowledge required to make sense of genetic test results for clinicians and patients. There seem to be no established protocols for choosing among the multiple service models.

3.3 There are many actions that can be suggested based on genetic test results.

Clinical decisions are the essential reason for ordering a medical genetic test. As a result of a test, patient management decisions can be made, ranging from changing drug dosage to suggesting a preventive procedure. However, explanations are sometimes necessary in order for health service providers such as health insurance providers to understand the value of a management intervention based on a genetic test. A genetic counsellor related: "Sometimes misinterpretation of genetic test results can occur, leading to misinformation." A thorough understanding of a genetic test result, including its limitations in predicting a health outcome, is critical for any healthcare providers in subsequent clinical decision making. Positive attitudes from interview participants were recorded in our study towards computational decision support systems (DSS) (incorporated with e-Referrals, order entry system, and clinical record system), particularly where they offer key functions, such as:

- To provide clinicians with genetic test utility information, e.g., information on disease risk probability, prevalence, penetrance, and cost/benefit of a test.
- To assess individual patient's disease risk and identify the patient/family at risk.
- To assist decision-making as to test or not to test.
- To support test referral process (according to protocols and possibly helped by e-Referral systems), e.g. for choosing a service model and checking test availability.
- To collect right information in referrals, e.g. family history information.
- To manage patients in complying with clinical guidelines, e.g. for drug dosage and surveillance.
- To check knowledge-bases and flag the patients for further intervention.

However, some health management decisions that are based on genetic tests are not agreed upon among healthcare professionals. An oncologist thought that

the ovarian cancer surveillance suggestions made by genetic counsellors would be a complete waste of time because such surveillance doesn't work.

In brief, we identified three issues in the clinical setting, i.e. the uncertain test utility, the multiple service models, and the difficulty in making clinical decisions according to test results. These three negative factors influence the clinician attitudes towards genetic testing and acting on test results. However, there is a discrepancy at clinicians' actual use of the technology.

3.4 Some routinely use genetic testing, while others don't.

The general view found in our study is that genetic testing in primary care is considered futuristic, but there is a sense that it will become part of everyday clinical work. However, no imperative is seen to anticipate any change in the foreseeable future, as expressed by a GP: "This is such a tiny aspect to GPs' work at the moment (I realise that it will increase in the future)." On the other hand, we met clinicians who have confidence and knowledge to utilize genetic testing in a safe and useful manner. They indicated that genetic testing is very valuable for diagnosis, treatment, assessing cancer recurrence risk, surveillance or preventative management, checking carrier status and pregnancy planning, lifestyle planning (e.g. in presymptomatic tests for Huntington's disease), and for avoiding adverse drug reaction. They either are pioneers and experts applying genetics knowledge in their specialties, or they are non-specialists but familiar with the contemporary development in the domain and are experienced with the test ordering pathways. Often through literature or colleagues, they have sought out what they feel to be adequate knowledge on medical genetics science as well as on the services system.

In summary, genetics science is not exact, nor is the body of knowledge complete. During the interviews it became clear that there exist mixed perceptions on the utility of genetic testing. The clinicians' attitudes towards using the technology are largely influenced by these perceptions. There appear to be gaps in clinicians' knowledge about the utility and availability of genetic tests, about disease risk assessment and referral processes, and about consequences of test results. These gaps present barriers for clinician involvement in genetic services delivery system and for improving healthcare outcomes through better clinical management based on genetic test results.

4 Discussion and Recommendations

There are multiple genetic services delivery models operating in New Zealand, each with inherent weaknesses, such as heavy dependence on clinician knowledge in the Patient-Doctor-Counsellor model and the Patient-Doctor-Lab Model, as discussed in an earlier paper [8]. Given this demand for clinician competence in order to deliver genetic services, we discuss the uncertainty in test utility and the associated clinician understanding of when and how to use genetic services, with recommendations to develop core competencies of service providers and to identify potential IT tools supporting them.

4.1 Know-how to use genetic testing

It appeared that some clinicians are routinely referring patients for genetic testing, while others see medical genetics as futuristic medicine. We found that the latter might not know enough about genetic testing, the processes to use genetic services, and how to deal with test consequences. This was reported in the UK as well [17, 18]. Literature has suggested an urgent need to train health professionals and develop their core competencies for genetic services delivery, but with little response to the call still [6, 19-21]. On the other hand, genetics is rapidly becoming part of everyday medicine; and clinicians will be required to establish an ability to obtain accurate family history, to identify people who could benefit from genetic testing, and to discuss with patients the core genetics concepts including probability and disease susceptibility [1].

The lack of knowledge among clinicians about genetic testing is closely related to the scarcity of appropriate information. There is a gap in delivering the critical information to clinicians; areas with an outstanding gap include: 1) evaluation results on clinical utility and health outcomes of genetic tests [1], 2) guidelines on ‘How much information of what nature should be required before genetic testing can be initiated?’ [22], 3) protocols and handbooks for genetic service referrals [20], 4) clinical guidelines on genetic disease management such as the UK National Institute for Health and Clinical Excellence (NICE) Clinical Guideline 41 on Familial Breast Cancer [23], and 5) policy frameworks around ethical dilemmas including ‘do no harm’ and ‘duty to warn’ the people at potential risks [24]. These findings have implications for genetics training in terms of medical curriculum review and development of continuing medical education programmes to improve from a current state where, internationally, new graduates

are often deficient in knowledge of genetics relevant for daily practice [25]. Our communications with the Auckland University medical programme director have found that over the last five years, genetics training has substantially increased particularly in terms of the basis of genetic testing, the value of genetic testing, the clinical scenarios that use genetic testing, the factors that affect uptake of genetic testing, and the ethical aspects of genetic testing. Moreover, our interview findings have implications for policy and legislation development, as well as presenting opportunities for knowledge management technology implementation. Targeting the information requirements, future IT implementation in the domain should be tailored to assist clinicians with key tasks such as risk assessment, test referral, and result interpretation.

4.2 IT support for genetic services delivery

There are numerous information sources constantly updating new discoveries in human genetics science. Navigations across such databases are offered by public portals such as the United States National Library of Medicine’s Entrez [26] and Unified Medical Language System Knowledge Source Server (UMLS/SKS), as well as commercial products such as SRS [27]. However, clinicians are often too busy to follow these sources and only need simple IT applications that incorporate genetics knowledge in their practice [28]. The disease risk assessment software used by genetic counsellors, such as BRCAPRO [29], may be too specific for primary or secondary care providers, especially in light of a low level of knowledge in the setting [1]. This presents a huge opportunity for DSS, as DSS can directly aid clinicians in clinical decision making by generating patient-specific assessments or recommendations [30]. DSS may be the answer to GPs’ request for clearer information about risk and prognosis, which was highlighted in our study. It should support clinicians in test referral decisions, taking into account the clinical utility of the test, the probability of disease risk, as well as the prevalence, penetrance, and cost/benefit of the test. In addition, DSS may provide information on the availability of genetic tests in the format of a user manual or “Lab Yellow Pages” [31], and achieve appropriate referrals by collecting the right information for genetic counsellors. It is critical for the success of DSS to provide recommendations rather than just assessments at the time and location of decision-making, i.e. aligning with clinicians’ workflow [32]. Applying up-to-date knowledge that links genetic tests to health management, DSS should aim not only to prompt referrals for testing, but also to translate test results into intervention

recommendations such as surveillance, treatment, and dosage. By assisting evidence-based medicine that uses genetic testing technology appropriately, DSS can provide clinicians with the knowledge to tap into quality healthcare delivery.

Another potential area is systematic support to facilitate processing the referrals for genetic testing. Technologies such as electronic referral systems (e Referrals) may help streamline the test referral, and referral triage, processes. Literature suggests that e Referrals can improve clinical effectiveness and cost-effectiveness [33], compliance with clinical guidelines [34], and in combination with electronic health records (EHR) systems, DSS and clinical guidelines, can streamline the referrals according to particular needs for different specialties and/or local hospital/region needs [35, 36]. Ideally, e Referrals would engender consistent business processes in genetic services, facilitate the tracking of appointments and tests status, and support the sharing of status information among service providers and users. Better information sharing and communication support would help bridge the conventional boundaries of primary, secondary and tertiary care, and ultimately would enhance the knowledge network [37] in genetic services delivery system. However, more work needs to be done to consolidate requirements and to explore user attitudes in this field. A UK study in cancer genetics concluded that computerized referral guidelines in primary care cannot be recommended for widespread use without further evaluation and testing [38]. On the other hand, the rapidly developing genetic testing technologies, such as next generation sequencing technology [39], may enable the sequencing of any patient's whole genome in the near future. This will add greater pressure on test referral processing and decision making as to test or not to test.

4.3 Study limitations

A major limitation of this study is that it is based on personal perspectives from individual experience, which might not represent accurately the entire New Zealand clinical genetic services system. The qualitative methods we used did not engage sufficient numbers of participants to create statistically significant data; and we were not using random sampling of a population but deliberately seeking individuals who enhance the diversity of our stakeholder group. To some extent, our small sample size is offset by the experience of genetic counselors and clinicians who have frequent direct interactions with large numbers of patients. The grounded theory approach with data saturation supported the research rigor. We have presented the New Zealand genetic ser-

vices as a case study, and although we have made some comparison to the broader set of literature and policies internationally, the extent to which the local experience may apply to other jurisdictions is left largely to the reader.

5 Conclusion

To leverage the power of genetic information it is necessary to understand the complexity of genetic testing and its use in the health system. Our grounded theory study discovered that a major barrier for involving healthcare providers in genetic services delivery is related to the uncertain clinical utility of genetic tests and the associated gaps in clinician knowledge regarding genetic testing. This presents an imperative for health IT innovators to target the problem of inadequate information available regarding test utility. Future IT implementation should focus on developing clinician competencies and supporting clinicians with key tasks, such as assessing disease risks, identifying the benefits and availability of genetic tests, streamlining referral processes, and managing patients according to test results. Technologies such as DSS and e-Referrals may empower healthcare professionals with knowledge and tools in order to deliver genetic services for better healthcare outcomes. We have presented the New Zealand genetic services as a case study, and while we have made some comparison to the broader set of policies and literature internationally, the extent to which the New Zealand experience may apply to other jurisdictions is left largely to the reader.

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