Clinical usefulness of genetic testing for drug toxicity in cancer care:

Decision-makers' framing, knowledge and perceptions

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Abstract

To explore the clinical uptake of pharmacogenetic/pharmacogenomic toxicity testing to reduce adverse drug reaction incidences, this paper analyses data collected through semi-structured face-to-face interviews with clinicians and/or clinician-scientists, primarily in the context of cancer treatment in multi-ethnic California (US), Vancouver (Canada) and Singapore. Recurrent themes in the data include the following: first, the scientific evidence for drug-gene interactions is perceived to be generally weak. Second, the primacy of medical treatment's efficacy over toxicity is the predominant frame through which clinicians consider testing. Third, physicians tailor their decisions according to each patient's tolerance levels for toxicity. Fourth, racially- and ethnically-based toxicity risk estimates are a factor shaping the clinical uptake of genetic tests, but they are controversial. These factors contribute to the low clinical uptake of toxicity testing for predictive purposes. We argue that the decision-makers' framing and perception are additional features to be considered in Hedgecoe's (2008) "clinical usefulness" framework.

Keywords: Toxicity, genetic testing, clinical uptake, race/ethnicity, framing, perceptions, evidence-based precision medicine

Introduction

Adverse drug reactions (ADRs) account for up to 33% of hospitalizations in the United Kingdom, United States and Asia (Budnitz et al., 2011; Zhou et al., 2015), and the termination of approximately 20% of investigational drug trials (Nelson et al., 2009). Toxicity testing has been demonstrated to be useful in reducing ADRs and associated hospitalizations for drugs such as abacavir (Moaddeb and Haga 2013; Phillips et al. 2001). A landmark study by Phillips et al. (2001:2275) found that "…more than half (59%) of the drugs cited in ADR studies are metabolized by at least 1 enzyme with a variant allele known to cause poor metabolism", which suggests that "the use of pharmacogenomics could potentially reduce ADRs, a problem of major significance" (ibid, 2277). A prospective observational study of ADRs in Singapore by Chan et al. (2016:1641) reported that "almost a third of ADRs detected in our study were caused by at least one drug with a PharmGKB CA [Pharmacogenomics Knowledge Base Clinical Annotation] for that ADR, suggesting that at least some of these ADRs could potentially have been predicted or avoided using pharmacogenomic testing". A genetic drug toxicity testing approach introduced in a Canadian primary care setting found that 97 percent of patients had at least one actionable genotype for medications to be included in a medication decision support system (Dawes et al., 2016). This demonstrates the severity of ADRs as a health threat and explains the push towards pharmacogenomics for improving the ADR situation.

According to Reiling and Evans (2015, 343):

> Current efforts that focus on the processes required to appropriately act on pharmacogenomic variability in the clinic are systematically moving pharmacogenomics from discovery to implementation as an *evidence-based* strategy

for improving the use of medications, thereby providing an important cornerstone for precision medicine" [emphasis ours].

However, the evidence base for genetic testing appears to be lacking. For example, Khan (2016:944) cautioned that while "one author has estimated that genotyping just for P450 would lead to a reduction in ADRs by 10% to 15%, this remains unproved."

It is perhaps unsurprising, then, consensus has yet to be achieved on incorporating toxicity tests into routine clinical practice as a standard of care (Marshall 2003). Some studies suggest that toxicity testing has potential to reduce ADRs (Amstutz et al. 2014; Evans and Relling 2004; Lemke et al. 2017; Moaddeb and Haga 2013; Phillips et al. 2001; Plumpton et al. 2016; Tan et al. 2010). Others have found that clinicians remain unconvinced and do not order such tests for various reasons (Collins, Carr, and Pirmohamed 2015; Dickmann and Ware 2016; Moaddeb and Haga 2013; Sanoff and McLeod 2008). This divide is starkly different from the general consensus towards toxicity tests. Hence, further study is needed to understand this consensus. In this paper, we combine the concept of "clinical usefulness" (Hedgecoe, 2008) with the concept of "decision frame" (Tversky and Kahneman, 1981) to address the following questions: (1) What factors shape clinical decisions whether to perform (or not) toxicity testing when prescribing drugs primarily for cancer? (2) Is the clinical uptake of toxicity testing affected by factors of racially and/or ethnically-framed population subgroup estimates, and if so, how?

Combining clinical usefulness with the framing of decision

With respect to clinical decision-making and genetics/genomics sciences, Rycroft-Malone et al. (2004) argued that, in addition to research-based evidence, it is important to recognize that three other types of evidence – clinical experience, patient experience, and

information from local contexts – contribute to evidence-based patient care. Hedgecoe (2008) pioneered the "clinical usefulness" (as opposed to clinical "resistance") framework in advancing a sociological understanding of the clinical uptake of genetic tests. Marshall (2003, 590) quoted a patient advocate saying that "I am mystified by the *resistance* to a simple blood test that might save children's lives" (emphasis ours). As such, Hedgecoe's intervention is important to remind us that the language we use to describe a phenomenon is important – in this case, understanding the uptake of genetic testing in the clinic is enhanced through the lens of the "clinical usefulness" of the test rather than clinicians' resistance to order the test. Hedgecoe (2008) further suggested several features of the clinical usefulness framework – clinicians' knowledge, differing interests of clinicians and researchers, how context influences the value of tests' accuracy, economic aspects of such tests and general cultural aspects of the clinic.

We use the clinical usefulness framework when examining the clinical uptake of pharamcogenetic/pharmacogenomics tests with respect to drug toxicity. Moreover, theoretically, we conceive assessment of clinical usefulness as a particular form of decision-making, and explore the concept of "decision frame" when analysing the empirical data.

In their path-breaking and now classic body of work on how decisions are made in uncertain situations, Tversky and Kahneman (1986: S265) argue that whether an object is chosen over another depends on "whether the relation of dominance is detected" and this, in turn, "depends on *framing* as well as on the sophistication and experience of the decision maker" (emphasis ours). In short, analysis of framing can help us to better understand factors shaping the decision-making outcome. This decision frame refers to "the decision-maker's conception of the acts, outcomes, and contingencies associated with a particular choice" (1981: 453).

That individuals' adopted roles lead to differences in decision frames is exemplified in Wagenaar and Keren's study (1986) on support for seat belt legislation. The authors found that participants in the role of parents were more likely to favour seat belt laws when presented with anecdotal information about a little girl who died in an accident but would have been saved had she been wearing a seat belt. On the other hand, participants in the role of public officials were more likely to favor such laws when presented with statistical information. In summary, social roles may lead to different framing of the same problem. As such, since this paper explores factors that influence use of existing toxicity tests in the clinic, we chose to pay particular attention to clinicians who order and use toxicity tests in real-world settings (as opposed to researchers who developed the tests).

Existing literature on genetic testing

Empirically, the development of pharmacogenetics products can be directed toward minimizing "adverse drug reaction" (ADR) – or in lay terms, serious side effects – of current pharmaceuticals by discovering genetic characteristics associated with those reactions. In this model, clinicians will not prescribe drugs to patients who are likely – due to genetic profile – to respond adversely. Existing empirical studies, primarily using literature reviews and survey methods, have noted five factors that shape clinical uptake of toxicity testing in various medical fields:

Factor one: lack of strong research-based evidence at the scientific level

Currently, randomized controlled trials (RCTs) are deemed the gold standard for clinical evidence, but there is a lack of RCTs for pharmacogenomics/pharmacogenetics toxicity tests due, in part, to funding and feasibility difficulties (Moaddeb and Haga, 2013). Moreover, although studies yielding statistically significant results were considered valid, their results

often could not be replicated. For example, there were conflicting conclusions on the clinical utility of toxicity testing for warfarin (Dickmann and Ware 2016).

Difficulty in establishing scientific evidence in gene-drug interactions is partly a function of the fact that ADR is not monogenic – the final outcome is shaped by the interplay of multiple genes and other non-genetic factors (Evans and Relling 2004; Sanoff and McLeod 2008). As such, while toxicity tests may show the presence of a certain genetic variant, drug selection/dosing based on genetic variability may not reduce ADR incidence, because genetic variation alone does not dictate a particular patient's drug response (Phillips et al. 2001). With warfarin, for example, although adjustments in dosing are recommended for different combinations of *CYP2C9* and *VKORC1* genetic variants (Bristol-Myers Squibb 2011), some studies have found that genetic polymorphism does not necessarily result in the toxicity phenotype. Intra-individual variability involving factors such as diet, concomitant drugs and comorbidity during the warfarin-maintenance phase is more likely to determine a patient's response (Dickmann and Ware 2016; Tan et al. 2010).

Factor two: pharmacogenomic knowledge gaps at the clinical level

As noted, clinicians' knowledge is one of the features of Hedgecoe's "clinical usefulness" framework. Several studies have surveyed physicians' adoption of pharmacogenomics testing (Stanek, 2012; Haga 2012; Taber & Dickinson 2014; Unertl et al. 2015). Haga et al. (2012) conducted a national survey in the US of a sample of primary care physicians (family medicine and internal medicine) and noted that "primary care practitioners envision a major role for themselves in the delivery of PGx testing but recognize their lack of adequate knowledge and experience" (p. 388). Taber and Dickinson (2014, 1) conducted surveys of primary care physicians, cardiologists and psychiatrists in the US and concluded

that “physicians continue to demonstrate pharmacogenomics knowledge gaps, and are unsure about how to use pharmacogenomics testing in clinical practice”.

Peterson et al. (2016) surveyed clinicians at an academic medical centre about their views on a large pharmacogenomics implementation, the PREDICT program, and concluded that “genotype results were valued for tailoring prescriptions, but clinicians do not agree on how to appropriately assign clinical responsibility for actionable results from a multiplexed panel.” (p.1) According to Zebrowski et al (2019, 9):

> In a study by Hamilton et al., physicians did not view genetic services as being advantageous or necessary for patient care; however, those physicians who were already versed and interested in genetic medicine were also more likely to implement it. Similar findings were echoed throughout the IGNITE study with interviewees expressing that clinicians seemed uncertain as to how genetic medicine would help their patients or provide benefit beyond current practice standards.

It is important to point out, however, that these survey results only capture what Collins and Evans (2007) refer to as “contributory expertise”, not “interactional expertise”. Building the electronic clinical decision-support system (CDS) is one solution proposed to address physicians’ knowledge gap. According to Klein, Parvez and Shin’s (2017, 2373) review, “the five common barrier categories [of clinical implementation of PGx] were as follows: scientific, education, ELSI, information technology and reimbursement.” The authors recommend ways to build the capacity of the clinical decision support system to “help recommend alternative medicines when a clinically high-risk drug is ordered” (p. 2374).

Factor three: tests’ costs, availability and logistics at the level of clinical experience

Even if physicians are knowledgeable about tests, cost has been highlighted as a top consideration (Peterson et al. 2016). Peterson et al. (2016, 4) found that “when deciding

whether to order a pharmacogenomics test, the most important considerations reported were strength of evidence for drug-gene interaction and patients' out-of-pocket costs...." According to the Washington State Healthcare Authority (2018, 2), "The cost of testing in U.S. prospective studies ranged from $175 to $475 in 2007 dollars." In Singapore, "patients requiring carbamazepine can potentially derive more benefit for no additional cost over the single HLA-B*15:02 test, which currently costs SGD200" (Chan et al. 2019, 408).

In their review of 47 economic evaluations of toxicity testing, Plumpton et al. (2016) found that it was cost-effective to conduct genotyping prior to administration for abacavir, allopurinol, carbamazepine, clopidogrel and irinotecan. However, cost-effectiveness of toxicity testing for a certain drug are often calculated based on information about a particular racially or ethnically-labelled subpopulation. For example, even though "there is professional consensus to test all abacavir-naïve patients prior to initiation" in the USA (Moadded and Haga, 2013, 162), one study conducted in Singapore specified that testing for *HLA-B*57:01* prior to administration of abacavir for the treatment of HIV was only cost-effective for "Indian" populations with a higher CD4 cell count on diagnosis (Kapoor et al. 2015). Framing the study of human genome variation using racial and/or ethnic categories has, however, been problematized. We shall return to this point in the section on racialization.

Logistical concerns such as availability and turnaround times of tests have also been raised as factors contributing to slow clinical uptake (Haga et al. 2012; Moaddeb and Haga 2013; Phillips et al. 2001). Haga and Moaddeb (2014, 140) note that "Major testing laboratories currently indicate that testing may take from three to 14 days to complete, a length of time for which some treatments may not be acceptably delayed." According to Cardinal Health's (2018, 16) survey in the US, "58% of the oncology survey respondents said that genomic testing was not available at their local institution, and 26% of the respondents said that turnaround time for

the testing is 15 days or more." The National Cancer Centre Singapore reported (2018, 4): "Results may take 2 weeks to 4 months, depending on the extent of testing".

Factor four: lack of clear guidelines and definitions

While biomarker information may be included in drug labels, not all such information is accompanied by required or recommended action; decisions on whom to test, when to test, which test to use, and what follow-up actions to take, are left to the discretion of healthcare providers (Dickmann and Ware 2016; Evans and Relling 2015; Gillis and Innocenti 2014; Moyer and Caraballo 2017). Recommendations may also differ across various sources of information (Dias et al. 2017). Furthermore, lack of standardisation in definitions of terms makes it difficult for physicians to make clinical decisions. For example, while the drug label for codeine suggests that it should be avoided in *CYP2D6* ultra-rapid metabolizers, "what is not clear in the drug label is exactly how the 'ultra-rapid' metabolizer should be derived from the genotype data" (Collins, Carr, and Pirmohamed 2016, 22).

Factor five: patients' perspectives

Tutton and Jamie (2013) noted that it is not just clinicians' perspectives that matter, but "public understanding of their clinical usefulness [is] also central to their uptake and routinization within healthcare practices." In Rycroft-Malone et al.'s (2004) words, "the personal knowledge and experience of patients and clients" is also a source of evidence that contributes to clinical practice. Taber and Dickinson's (2014, 5-6) US-based survey reported:

> when those who indicated that they had not ordered a pharmacogenomics test in the past year were asked why they had not, the most common answers were not knowing what test to order, lack of insurance coverage and uncertainty about the clinical value of the test. Other answers were not applicable to patients, patient declined test and

privacy concerns (p. 5). Those who indicated that they did not plan to order a pharmacogenomics test in the next year were asked why they would not. The most common responses were similar to reasons cited for not having ordered a test in the past year 76.8% indicated that they would not know what test to order, 62.9% indicated that they would be uncertain of the test's clinical value, and 48.3% indicated that insurance would not cover the test. Other responses were not applicable for patients, patient likely to decline test, and privacy concerns. (p. 6).

Racialization of pharmacogenetics/pharmacogenomics drug toxicity studies

The construction of racial and ethnic populations/publics in genomic science and its consequences have been the subject of extensive study (Benjamin, 2009; 2015; Bliss, 2011; Duster, 2015; Hinterberger, 2012; M'Charek, 2013; Nelson, 2016; Williams, 2018). For example, Hinterberger (2012) highlights how a group French settlers who lived in the territory now known as Quebec was transformed into a genetically homogeneous population by a diverse set of genealogists, historical demographers, epidemiologists and geneticists working for a private pharmaceutical laboratory in Quebec, indicating that the idea of the founder population is significantly contested. Populations demarcated along racial, ethnic or ancestry lines, whether constructed through the latest statistical algorithms to divide human samples in the lab, or presented as boxes to tick on a national census, are what M'charek (2013) called "technologically assisted categories".

The "invisibility" of non-biological processes in the making of racial and ethnic categories means that it would be inaccurate to use them as if they were accurate biological categories for drug prescriptions (Bowker and Star, 1999). Nonetheless, Klein, Parvez and Shin (2017, 2368) claimed that "ethnicity has been recognized as the main factor that contributes to inter-individual variability in drug response." Numerous studies have also demarcated

differences in drug-related enzymes along racial and/or ethnic lines (Bonham, Callier, and Royal 2016; Dong, Sung, and Finkelstein 2012; Evans and Relling 2004; Kapoor et al. 2015; Tan et al. 2010). One reason for the continued use of race involves sets of regulations in different countries for race-based/ethnicity-based record-keeping for research and clinical care (Epstein, 2007; FDA, 2016; Lee, 2012; Ramamoorthy et al., 2015).

The issue of race has been a problem for pharmacogenetics since the very beginning (Jones and Perlis, 2006; Jones, 2011). Hence, in this paper, we explore the clinical implications of pharmacogenetic/pharmacogenomics studies using racially- and ethnically-based population subgroups. Some people might believe race-/ethnicity-based toxicity risk estimates can be used instead of genetics-based risk estimates derived from genetic testing. For illustrative purposes, we focus on examples involving three drugs: carbamazepine, warfarin and irinotecan.

Carbamazepine

Carbamazepine is an anticonvulsant/antiepileptic drug which has been associated with various types of adverse reactions, such as skin reactions (48%), haematological disorders (12%) and hepatic disorders (10%) (Askmark and Wiholm 1990). Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are among the skin reactions commonly noted with carbamazepine, and these disorders "carry a mortality [rate] that can be as high as 30% and require early diagnosis, with prompt withdrawal of all suspected causative drugs" (Ferrell and McLeod 2008). Since 2007, the FDA has made labelling changes for carbamazepine. Owing to data implicating the *HLA-B*1502* allele as a marker for carbamazepine-induced SJS and TEN (Chen et al. 2011; Chung et al. 2004; Ferrell and McLeod 2008; Locharernkul et al. 2008; Mehta 2009), the latest label for carbamazepine approved by the FDA (Novartis Pharmaceuticals 2009, 4) recommends genotyping patients "with ancestry in populations in which *HLA-B*1502* may be present"; on the same label, the FDA noted that the *HLA-B*1502*

allele is prevalent in individuals of Asian descent but "largely absent in individuals not of Asian origin (e.g. Caucasians, African-Americans, Hispanics, and Native Americans)", although the FDA also acknowledged that prevalence rates varied notably across "Asian" populations. The category of "Asian," more fundamentally, has been shown to vary across time and place (Goodman, Moses, and Jones 2012).

Health Canada and Singapore's Ministry of Health (MOH) and Health Sciences Authority (HSA) also issued letters to medical professionals in their respective countries, recommending genotyping for *HLA-B*1502* prior to initiation of carbamazepine therapy in new patients of "Asian" ancestry as a new standard of care (Health Canada 2008; HSA 2013a). However, Canadian authorities also cautioned:

> Health care professionals should also be aware that HLA-B*1502 genotyping as a screening tool has important limitations. These limitations include the possibility that serious dermatologic reactions may still occur in some patients who test negative for HLA-B*1502 and that some patients who test positive for HLA-B*1502 may not develop serious dermatologic reactions. This suggests that the presence of the allele may be only one of the risk factors for developing serious dermatologic reactions. Therefore, HLA-B*1502 genotyping must never substitute for appropriate clinical vigilance and patient management. (Health Canada, 2008).

Nonetheless, Singapore's HSA remains firm in its decision to mandate HLA-B*1502 genotyping, and asserts that a local HSA-initiated multi-centre study conducted in various hospitals in Singapore and international data supports a strong association between *HLA-B*1502* and carbamazepine-induced SJS/TEN (HSA 2013b). As articulated by White et al. (2017, 47):

> Carbamazepine and allopurinol are two of the most common causes of SCARs in Singapore and the risk alleles associated with carbamazepine- and allopurinol-SCARs (HLA-B*15:02 and HLA-B*58:01, respectively) occur at high frequency in the Singapore population. In 2013, the primary regulatory body in Singapore, the HSA, in conjunction with the Ministry of Health recommended HLA-B*15:02 genotyping before initiation of carbamazepine as standard of care for new patients of Asian ancestry. Following this recommendation, only 1 case of carbamazepine-associated SJS/TEN in 4 years has been reported, a marked reduction in incidence from the pretesting baseline of approximately 18 cases per year.

Irinotecan

Irinotecan is used to treat a variety of cancers. The main adverse effects associated with irinotecan are neutropenia and diarrhoea (Armand et al. 1995). Several published studies have argued that a disposition towards irinotecan-induced toxicity is associated with various *UGT1A* polymorphisms, which have different prevalence across ethnic groups (Chowbay et al. 2001; Jada et al. 2007; Liu et al. 2014). For instance, Sung et al. (2011, 1173) emphasizes:

> in Singapore, the genotypes UGT1A1*28/*28, *6/*6 and *6/*28 that are associated with elevated risk of irinotecan induced neutropenia are found in 9.7% of the Chinese population, 5.0% of the Malay population and 18.7% of the Indian population. This compares with 11.5% in North American Caucasians and 8.1% in Japanese. With the Singapore Indian population having nearly a one in five chance of carrying one of these high-risk genotypes and Singapore Chinese having a one in ten chance, in 2009 the HSA (Health Sciences Authority) requested that irinotecan manufacturers revise the package insert to include the pharmacogenetic association with severe

neutropenia, and publicized the association and availability of a genotyping test at the NCC (National Cancer Centre)".

The National Cancer Centre of Singapore (NCCS) further noted in a media release: "certain ethnic groups (e.g. Indians) may be more susceptible to increased toxicity when administered Irinotecan and that prior testing of their UGT1A1 genetic constitution can aid in the selection of a right dose to match the individual's metabolic capacity and hence alleviate the risk of toxicity" (NCCS 2010).

Warfarin

Warfarin, the most commonly used oral anticoagulant for thrombosis-related complications, is associated with risks of major bleeding (Wigle et al. 2017). Variations in two genes, *VKORC1* and *CYP2C9*, are two of the more well-known genetic polymorphisms associated with warfarin metabolism (Bristol-Myers Squibb 2011).

However, the practical usage of such pharmacogenomics-guided dosing recommendation is limited. As of March 8, 2018, the Centers for Medicare and Medicaid Services concluded on its website that "the available evidence does not demonstrate that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness improves the outcomes in Medicare beneficiaries" (Centers for Medicare and Medicaid Services, 2009). Indeed, a warfarin maintenance dose has been found to be affected by the variant genotype of genes beyond *VKORC1* and *CYP2C9*, and non-genetic factors like age, body weight and clinical conditions (Kumar et al. 2014).

Nonetheless, several studies indicate that the prevalence of *VKORC1* and *CYP2C9* polymorphisms vary among ethnic groups, and can account for about 30% of variance in warfarin dose response (Fung, Patsopoulos, and Belknap 2012; Limdi et al. 2015). This has led to the development of a number of pharmacogenomics-guided, race-based dosing algorithms, such as that by Tan et al. (2010, 442), which suggested that "Chinese patients are known to be more sensitive to warfarin and require a 40 to 50 percent lower maintenance dose of warfarin when compared with Europeans, while the African-American population requires a higher maintenance dose". Similarly, the drug label approved by the FDA (Bristol-Myers Squibb 2011, 23) states that "Asian patients may require lower initiation and maintenance doses of warfarin".

Methods

As noted, the majority of existing studies on the clinical uptake of toxicity testing are survey-based single-country studies. Given the global scale of genomic science and precision medicine, however, we believe it is important to understand clinicians' experiences using qualitative research methods with semi-structured interviews to provide contexts and grounded understanding of the clinicians' views and opinions, in places where precision medicine is more advanced (the USA and Canada), and those to which it has disseminated (i.e. Singapore). Given this study's research question on the usage of race/ethnicity as a surrogate for genetics and pharmacogenomics toxicity testing ordering, it is important to understand the racial/ethnic composition of the populations in these countries.

United States

The United States' Census Bureau adheres to the 1997 Office of Management and Budget (OMB) standards on race and ethnicity in classifying self-identified racial categories

(United States Census Bureau, 2018). The OMB requires that race data be collected for a minimum of five groups: White, Black or African American, American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander. The OMB permits the Census Bureau to use a sixth category - "Some Other Race," so that respondents may report more than one race. The concept of race is separate from that of Hispanic origin, so that Hispanics are separately captured under the five official racial categories. In 2018, White Americans formed a majority at 76.5%, while African Americans (13.4%), Asians (5.9%), American Indians and Alaska Natives (1.3%) and Native Hawaiians and Other Pacific Islanders (0.2%) made up the rest of the population (U.S. Census Bureau, 2018). Since implementation of the Affordable Care Act (ACA) health coverage expansions in 2014, "people of color" have experienced large coverage gains that have helped narrow longstanding disparities in access and affordability of healthcare amongst the various ethnic groups (Artiga, Orgera, and Damico, 2019).

Canada

The Public Health Agency of Canada includes race in its mandated reporting on health disparities, and the Canadian Institute for Health Information reports on disparities in health care and health outcomes, with a focus on lower-income Canadians (Canadian Institute for Health Information, 2015). In 2016, over 250 ethnic origins or ancestries were reported . Four in ten people reported more than one origin, with the British Isles and France the most common. About 2.1 million people, or 6.2% of the Canadian population, reported Aboriginal ancestry (Statistics Canada, 2017). Chinese ancestry (1.8 million), East Indian ancestry (approximately 1.4 million) and Filipino ancestry (837,130) are among the 20 most common ancestries reported (Statistics Canada, 2017).

Singapore

Singapore's Ministry of Health has overall responsibility for health care, setting policy direction, managing the public health care system, and ensuring quality of care and its responsiveness to residents' needs. The Ministry of Health regulates the health care system through legislation and enforcement (MOH, 2015). Among its core regulatory functions are licensing health care institutions under the Private Hospitals and Medical Clinics Act and conducting regular inspections and audits (MOH, 2015). As of the end of June 2018, Chinese made up 74.3% of the resident population. This was followed by Malays at 13.4% and Indians at 9.0% (Department of Statistics, Singapore, 2018).

There are medical centres in California (US), Vancouver (Canada), and Singapore practicing precision medicine, and we approached a scientist and/or clinician-scientist at each to begin data collection. At the conclusion of each interview, we asked the clinician/clinician-scientist to recommend another clinician/clinician-scientist who had experience with precision medicine and might be willing to talk to us. This practical way of gaining access to respondents has theoretical as well as methodological advantages. We were referred to clinician/clinician-scientists who had experience with genome-based personalized medicine; thus, we did not speak with clinician/clinician-scientists who had only heard of precision medicine but did not have experience with it.

In the end, semi-structured interviews were conducted with a total of 46 subjects, who were identified using the snowball sampling technique, regarding research and clinical decision-making experiences with precision medicine (ten scientists and/or clinician-scientists were interviewed on the West Coast of the United States, eleven in British Columbia Canada, and 25 in Singapore). Snowball sampling is a multistage technique that begins with one or a few people or cases and spreads out on the basis of links to initial cases. This technique is appropriate to select members of difficult-to-reach, specialized populations. Interviews were conducted face-to-face in a public space chosen by the interviewee according to their

convenience. Interviewees were assured of privacy and confidentiality. Each interview lasted between 45-60 minutes. All 46 interviews were audio-recorded and transcribed verbatim.

The semi-structured interview schedule for all interviewees started with general questions such as: (1) "what is your own view of potential issues and challenges of using genetic testing to tailor medicine – genetic testing for determining next steps for treatment (either testing the tumour's somatic mutation or the SNP-profiling for predicting drug toxicity)?" (2) "There are a growing number of human genomic studies on ethnic or racial differences in drug responses and disease susceptibility. In your view, what is the likely impact of these population-based genomic studies"? We followed the general questions by bringing up examples of published articles to discuss with interviewees. The articles were sometimes authored by the interviewees, because they were clinician-scientists.

Data analysis followed systematic procedures that moved from narrow units of analysis (e.g. significant statements) to detailed descriptions that focused on two elements, "what" individuals have experienced and "how" they have experienced it. This thematic analysis was achieved through manual analysis of transcripts by two researchers (Y.L. and Z.O.) in a six-step process adapted from Braun and Clarke (2006).

The study was approved by the Nanyang Technological University Institutional Review Board. In the following paragraphs, we describe themes that we see when we systematically analyze the interview data across the three settings, but we do not claim that the findings are "representative". Interviewees are referred to by pseudonyms (Dr. 1, Dr. 2, etc.) for confidentiality.

Results

Interviewees were generally aware of pharmacogenetic/pharmacogenomic toxicity testing, and expressed interest due to its promised benefits:

> Now the way we dose is very crude, based on height and weight. … If there is a way to understand all the dosing and changes and who is going to be more sensitive and who is going to be less sensitive, I think that is of interest. (Dr. 8, Canada)

> …if you don't test for it, patients get some serious toxicity and they may be occupying a bed for one month, two months and they may even die from it. Coupled with the treatment cost and all that, hospitalization cost, it's a lot. Whereas...you just spend a couple of hundreds testing for the drug [toxicity]…. And another thing about doing pharmacogenomic testing is that these polymorphisms are germline [i.e. mutations that are throughout the body and can be passed down to the offspring, in contrast to somatic mutations in the cancer cell]…. So once the test is done, the test can be applied over and over again…. (Dr. 37, Singapore)

Two physicians explicitly recognize the potential of toxicity testing to identify at-risk patients, as it would allow them to prospectively take action to avoid ADRs.

Despite recognition of its potential benefits, toxicity testing is "not [the] standard of care right now" (Dr. 40, Singapore). This is unlike pharmacogenetic/pharmacogenomic testing for drug efficacy, which has become the standard of care in several contexts, such as *EGFR* mutation testing in non-small cell lung cancer and *HER2* mutation testing in breast cancer patients. This difference is reflected by interviewees from all three countries. Specific reasons are presented in detail in the section below.

Not utilizing toxicity testing

The low uptake of toxicity tests prior to drug prescription can be attributed to the low perceived usefulness in helping to shape an optimal personalized treatment plan. This can could be due to a number of factors.

(1) Clinicians' perception of lack of strong research-based evidence and knowledge of the complexity of the drug toxicity phenotype

Interviewees point out cases in which detection of the genetic variant does not translate into toxic side-effects, or in which toxic side-effects occur in the absence of the genetic variant:

> The other thing is it doesn't predict with certainty. It predicts the toxicity but a lot of people [suffer] toxicity from irinotecan and they are not polymorphic; they don't have the UGT1A1 variant and they still have significant toxicity from Irinotecan. (Dr. 14, US)

> … just because you get the allele doesn't mean you're going to get Stevens-Johnson syndrome [from carbamazepine]. There is only about a 5-8% chance. So that means most of the people that are not taking it, as a result of their positive test results, could have tolerated the drug just fine. (Dr. 11, Canada)

> … the differential is that people, the normal allele, maybe 20%, [of developing the toxicity phenotype] and the people who are with the heterozygous alleles are, the variants, are maybe 30%. So it's not big enough for you to change your [irinotecan] treatment…so basically you get the result back, you're not sure what you're gonna do with it, that's why we don't get the test. (Dr. 40, Singapore)

Interviewees consider genetic testing for toxicity a "brand new field" (Dr. 5, Canada) that is "still somewhat controversial" (Dr. 40, Singapore) as there has yet to be "a single SNP [single nucleotide polymorphism] that tells me whether you are going to have bad toxicity [as clearly as an EGFR mutation]" (Dr. 16, US). While both pharmacogenetic/pharmacogenomic testing for toxicity and that for drug efficacy are founded upon the same basis of genotype-

phenotype correlations, the perceived lack of discriminatory power in toxicity tests does not instil sufficient confidence in physicians.

The underlying reason for the perceived lack of discriminatory power in existing toxicity tests lies in the nature of drug toxicity as a complex phenotype. The relationship between genotype and occurrence of ADRs is "not one genetic variant and one ADR; it's probably multiple genetic and clinical factors and the dose that you're on and the combination of medications, all of that together probably makes the reaction occur" (Dr. 11, Canada). Dr. 8 (Canada) illustrates the complexity of drug toxicity as a phenotype using warfarin as an example:

> If we look at warfarin, your [toxicity] levels are going to be affected by whatever pharmacogenomic says. It is also going to be affected by your diet. … I don't think that is totally understood…. So this [toxicity testing] is kind of measuring one factor, but it is not the whole story…. There are multiple enzyme[s] and genes involved in metabolizing drugs.

Several factors contribute to ADRs. This makes accurately pinpointing the risk level of developing ADRs and the severity of toxicity for each individual difficult. It also means that standardized guidelines, if any, must be able to account for many possible circumstances:

> Patients who are either heterozygous or homozygous, also have increased risk of toxicity from Irinotecan. … [I]t's a spectrum. So it's not an absolute indication, this is very well-studied in the literature and well-reported that there is no clear safe dose for one patient versus another. (Dr. 15, US)

> Even if you have this [SNP], should you halve the dose? Should I omit it completely? (Dr. 43, Singapore)

In other words, such guidelines, with the level of nuance required to address every situation, are difficult to achieve.

(2) Clinicians' decision frame: Prioritizing pharmaceuticals' efficacy over toxicity and ethical dilemmas

Physicians have to consider implications of utilizing a toxicity test. One concern is the delay of treatment that may occur as a result of waiting for test results to be returned:

> …it's the severity of the toxicity, it's the cost of the test, it's the wait time of the test … does that delay treatment if we're waiting for the test, and again if you get the test, and it's predicting...an adverse event, *do you forgo the treatment*? (Dr. 15, US)

In a clinical context in which no alternative drugs are available, toxicity tests are useless because "besides this medicine, you don't have any other choices" (Dr. 29, Singapore) and "until you can cure most diseases, you don't have the luxury of saying that [we can] cure them with less toxicity" (Dr. 5, Canada). Without alternative drugs that can act as substitutes, physicians will end up using the same drugs regardless of results, thereby reducing the incentive to order toxicity testing even if it is available. For some diseases, however, alternative treatments may be available. In those situations, knowing a patient's predisposition for toxic side-effects may be useful, as physicians "may be able to intervene and say that [because] you are at high risk of getting neutropenia with these, we want to give [you a] GCFS [Granulocyte colony-stimulating factor] for your treatment" (Dr. 5, Canada).

Even in the presence of alternative treatments, however, physicians have to grapple with the dilemma of the possible trade-off between efficacy and toxicity. Should the results of a toxicity test indicate that a patient has high risk of ADRs with a particular drug, physicians can choose to replace the original treatment plan with alternatives such as changing drug

options or dosing. But, the possibility exists that efficacy of the alternative therapy is not as high, which may negatively impact the treatment outcome for the patient:

> …of course you use a different dose you get a different effect and maybe you don't see the efficacy. (Dr. 26, Singapore)

> The other argument against it is you forgo a potentially … beneficial therapy because you detected it [the genetic marker], even though … detection of the deficiency does not 100% correspond to the toxicity. (Dr. 15, US)

> Whether changing doses based on those SNPs has benefits in terms of potentially less toxicities in patients with certain SNPs, but at the potential risk of less efficacy in those people. (Dr. 8, Canada)

The efficacy vs. toxicity distinction is an important theme, and we provide a fuller and more nuanced understanding of why oncologists do not routinely adopt pharmacogenetic toxicity testing in the clinic. In short, even in the presence of alternative treatments, physicians may not use toxicity testing due to potential delays to treatment and lack of confidence in results, as well as lack of clarity on how a treatment plan should be modified for a particular patient based on his/her results and how any modification may affect treatment efficacy.

In light of all of these limitations, most interviewees stated that availability of toxicity tests has not been practice-changing, and that existing methods are actually good enough:

> …even if you know [the] FDA approves tests like UGT1A1, it is something for irinotecan-induced toxicity, nobody is using it in average populations. In certain cohorts, they do. But it is under-utilized at the very least. … [O]ncologists are trained to know exactly what to do, based on side effects, how the dose is adjusted, pretty much [what]

we are trained to do. So it can be seen as … more [of an] academic problem than [a] real problem. (Dr. 14, US)

In addition to the example of irinotecan mentioned above, as far as using warfarin is concerned, the goal is still to end off with a therapeutic international normalized ratio (INR), and the physicians remarked that the existing method was sufficient to achieve that goal.

(3) Physicians' and patients' expectations in the context of treating cancer

While researchers focus on developing pharmacogenetic/pharmacogenomic tests for drug toxicity as a way to achieve precision medicine, physicians have remarked that genetic information, although helpful, is but one part of clinical judgement. For physicians, a key element of medicine is taking into account the patient's personal expectations and experiences:

I will just deal with side effects later to be honest. … I think our cancer patients recognized that treating cancer is going to be toxic…but they are willing to take that risk because they obviously have a very serious disease that they want to treat…. [I]f you have a horrible rash, nobody is going to take it, but in this case, because you are using a drug that potentially can extend your life from six months to two years, they want to take that. (Dr. 16, US)

His [the patient's] goal of treatment may be different from somebody else's…. For example if a patient [is] unwilling to come to [the] hospital...many times, repeatedly for toxicity. … And [is] willing to accept a less[er] response by lowering the dose, that's personalized to him! … It's different from somebody else who says I don't care what toxicity you give to me, just give me the biggest dose that you think is safe …. (Dr. 26, Singapore)

In other words, patients' toxicity tolerance and treatment goals vary. Consequently, clinical action taken will also vary from patient to patient as a result of interaction between the patient and his/her clinician. This is especially so in cases of severe diseases like cancer, when stakes are higher. If a patient is willing to risk ADRs regardless of genetic propensity for toxicity for higher chances of treatment efficacy, physicians might find it unnecessary to order toxicity testing.

(4) Pros and cons of race-based estimates

As noted above, the advent of the genomic era offers the opportunity to fine-tune treatment decisions based on each individual's unique genomic profile instead of racial/ethnic identity. Yet, it appears that some clinicians and/or clinician-scientists believe that race/ethnicity still has a role to play in managing toxicity. Some interviewees mentioned that racial/ethnic differences continue to be used, particularly in deciding whether to send someone for toxicity testing:

> If you're doing cost-benefit analysis, and you identified that if you take [everybody], there's no benefit about broad testing. But in this high risk patient population, maybe it is [cost-effective]…. None of these drugs benefit everybody…. [C]an you figure something that predicts for response or toxicity that indicates your clinical decision making in one direction or another? So, to me it seems perfectly reasonable that if you identify that African Americans were at a higher risk for toxicity from this particular drug, maybe that's the subpopulation that you do a broad testing in. (Dr. 15, US)

> …knowing the [racial/ethnic] ancestral background, this is an opportunity to check for those variants in that child, because we know that the potential for toxicity exists before we begin. So we wouldn't begin on the same dose, or the same way. (Dr. 11, Canada).

> The consultant always tell[s] me that [for] Indians, you have to use higher doses. Okay, otherwise you [will have a problem] and indeed I always remember this patient of my senior consultant who has doses as high as 8mg warfarin, which I hardly ever see, you know, 6 to 8 mg. Usually among the Chinese, it will be 2mg, 3mg, sometimes 4, and this guy is 8mg and is still walking around, you know, and still not well-controlled. So already we knew there was some racial differences. (Dr. 29, Singapore)

In other words, another way of predicting toxicity is to use a patient's racial/ethnic identity to estimate likelihood of developing ADRs.

However, there is an increasing recognition that racial/ethnic categories are not precise enough. Such broad population-based categories cannot sufficiently address the inherent heterogeneity of populations:

> We also know that toxicity may be different if it's an Indian in Asia versus someone who is Indian American. You know because there are these certain things that change with migration. (Dr. 17, US)

> I think ultimately it is simplistic to say that Asians may get more toxicity…. Asians are not a homogenous group of people and it may be also true that Polish Caucasians are at a higher risk of neutropenia. But then if you have someone Polish … marry someone Irish, you dilute that effect. So ultimately I think studies are of interest, but I think they have limited value in terms of applicability to individuals. (Dr. 5, Canada)

> Because it's…not a[n] all-or-nothing principle. It's not [that a] drug is effective or not effective, toxic or not toxic. It's always a normal distribution curve or there's always a distribution...so…It should be based on the individual, where he stands…in that

distribution curve. So I don't think there should ethnic-based [interventions]. (Dr. 26, Singapore)

While there may be different frequencies of a genetic allele across different racial/ethnic populations, these population-based comparisons are averages derived from a heterogeneous population that fail to account for environmental and social factors, which can differ between two individuals of the same racial/ethnic group, and can change across a person's lifetime. Extrapolating these population averages to deduce an individual's specific genetic profile introduces inaccuracies. Hence, interviewees caution against simply using race/ethnicity to make medical decisions.

Post-diction/retrospective use of toxicity tests

Only two out of 46 interviewees noted that they used toxicity tests for understanding causes for adverse events in the clinic:

DPD [Dihydropyrimidine dehydrogenase] is only when we run into trouble, which is pretty much standard because the genotype test is only about 50% accurate. … [So, it helps when we run into trouble with toxicity], then we go back and prove there was [the polymorphism]. (Dr. 14, US)

One of my patients I gave 5-FU, massive neutropenia for almost three months, so I say, "Can you guys just check the germline for like DPD?" and they actually found an unusual SNP variant and actually, that probably explained why she had 5-FU toxicity. (Dr. 3, Canada)

While a small number of physicians in this sample do utilize toxicity testing in the clinic, more often than not it is to offer a possible explanation (and therefore assign blame) for adverse events, instead of prospectively predicting for risk of ADRs. Similarly, Amstutz et al. (2014,

503) discussed at length a case in which clinicians discontinued carbamazepine for an Asian patient because they thought her rashes were signs of SJS/TEN, given her race, and gave her another medication. However, because she had seizures again, the physicians genotyped her, and realised that she did not have 1502 and put her back on carbamazepine. This is a case in point about using race/ethnicity as a surrogate for genotyping and using the genetic testing retrospectively for managing ADRs, indicating that postdiction toxicity testing occurs beyond our sample.

Discussion

This paper intends to address two questions: 1) what factors shape clinical decisions whether to perform (or not perform) toxicity testing when prescribing drugs primarily for cancer? (2) Are racially or ethnically-framed population subgroup toxicity estimates a factor in shaping the clinical uptake of toxicity tests, and if so, how? Based on a thematic analysis of the interview data collected in Singapore, western Canada and western United States, we elaborate on factors limiting the "clinical usefulness" of predictive toxicity testing, showing that clinicians sometimes use toxicity tests for "postdiction" purposes instead, and document conflicting views concerning toxicity risk estimates based on racial and/or ethnic population subgroups to determine whether testing is performed.

The theoretical contributions of this paper are on two fronts: first, we add the concept of decision-frame to studies of clinical usefulness of genetic tests. Empirically, to the best of our knowledge, this is the first paper to extend Hedgecoe's "clinical usefulness" framework to examine pharmacogenetic toxicity testing in the clinic; previous studies were concerned with the clinical uptake of drug efficacy testing. While Hedgecoe (2008) found the primacy of clinical judgement over scientific evidence as part of the reasons for low clinical uptake of drug

efficacy testing, our paper suggests that the primacy of drug efficacy over toxicity concerns result in low clinical uptake of drug toxicity testing. Consistent with existing literature, we found that the lack of strong research-based evidence in pharmacogenetic/pharmacogenomic toxicity studies, as well as cost, availability, and logistical concerns are key factors limiting toxicity tests' clinical utility in oncology. Moreover, our findings indicate that clinicians have interactive expertise with pharmaceutical sciences, and are knowledgeable about the complexity of the toxicity phenotype and the drugs they use.

While Nelson (2016) reveals various social forces surrounding the spectacular popularity of the usage of genetic testing for ancestry, this study documents the lukewarm reception of genetic testing for drug toxicity primarily among oncologists. Rycroft-Malone et al. (2004) argue that physicians' practice-based tacit knowledge as a source of evidence is crucial in understanding clinical decision-making. In other words, the idea promoted by advocates of targeted drugs and genetic testing is that scepticism and resistance stem from a lack of knowledge. However, what we have found in studying the clinical uptake of toxicity genetic testing is similar to what Hedgecoe (2004) demonstrated in genetic testing for drug efficacy; that is, clinicians are knowledgeable; yet despite this, they remain doubtful and uncertain, and have a number of ethical reservations. We conclude that our interviewees' ambivalence towards using DNA analysis for managing adverse drug reaction result from the primacy of treatment efficacy and the ethical dilemmas oncologists face in relation to the state of the medical care, including, but not limited to, the therapeutic desperation, the (non) existence of alternative drugs, the expectations of relatively high toxicity in cancer treatments, the trade-off between drug efficacy and toxicity, and efficacy of existing methods. As such, we argue that, decision-makers' framing and perception, in addition to their knowledge and interests, are theoretically important factors to be considered in advancing Hedgecoe's (2008) "clinical usefulness" framework for genetic tests. To put this differently, even if tests do predict

for toxicities accurately, these tests are still not clinically useful enough to be adopted because results often cannot be translated into treatment changes without compromising priorities of first and foremost treating the patient.

We also found that, while clinicians may not use toxicity testing to solve the problem of ADRs, they use it sometimes to provide an explanation for the problem. The significance of this finding is that, while clinicians may know and articulate the complexity of causes of ADRs, the fact that they attribute the genetic cause to ADRs, ironically and inadvertently contributes to genetic determinism.

Secondly, as far as we know, this is also the first paper to examine to examine whether a patient's perceived race/ethnicity is used as a surrogate for genetic information during clinical decision-making about drug choice and drug risk. Existing studies on drug efficacy and race have shown that population groups can be strategically appropriated by interested parties to the detriment of the health care of individuals designated as members of said groups (Kahn 2013; Roberts 2011). Conceptually, M'Charek (2013: 421) argues that "race is not a singular object 'out there' in nature, but a relational entity enacted 'in here'", and suggests "a turn to practice to examine what race is and how it is made relevant". Our study examined the practice of pharmacogenomics toxicity studies and testing, and demonstrated the multiplicity of race in this context. Like Williams (2018), our study also found that the interviewees' use of "the world of referents that hint towards race – for example, 'population', 'ethnic group', 'ancestry' and so on – speak to race's multiplicity" (p. 26). Williams (2018) showed that race oscillates "between the status of vital information to the life of a public stem cell inventory, and of secondary data that provides little useful information to clinicians selecting tissue" (p. 24). In a similar vein, we found that clinicians disagree on the usage of patients' race/ethnicity as a surrogate for genetics. Those who support the use of pharmacogenomics toxicity studies using

race/ethnicity-based population subgroups to inform clinical decision-making tend to base their arguments on probabilistic grounds. In sharp contrast, those who oppose such usage point out that racial/ethnic categories are not precise enough to make clinical decisions – since there is genetic heterogeneity within such population groups, it will be incorrect to use a patient's racial/ethnic identity as a shortcut. The uncritical acceptance of the usage of race/ethnicity in pharmacogenomics toxicity studies by the former group we might call it "pragmatic racialism" vis-à-vis what Bliss (2012) calls "antiracist racialism". However, it is perhaps more important to highlight the latter group of "biodefectors" (Benjamin, 2016, p. 968). Indeed, even when talking about "founder populations," as Hinterberger (2012, p. 82) demonstrated, "the emphasis on the homogeneity and purity of the Quebec founder population…is laden with historical negotiations of racialized population mixing in the settlement of new world." Benjamin (2016), who pioneered and articulated the notion of "informed refusal", suggested that we situate refusal "within a more comprehensive spectrum of human agency vis-à-vis technoscience, in which institutions are called upon to consider how their own norms and practices, as well as existing social hierarchies, place pressure on people to defer to authority" (p. 971). Although some of our interviewees' "informed refusal" to use racialized statistics in clinical decision-making for the individual patient reflects a certain level of human agency vis-à-vis technoscience, we suggest that the finding prompts us to reconsider the ways in which population-based genetic/genomic datasets are collected, labelled and analyzed along racial/ethnic lines at the institutional level.

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