Why the Shift? Taking a Closer Look at the Growing Interest in Niche Markets and Personalized Medicine

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Pharmaceutical research and development is increasingly focused on niche markets, most notably treatments for rare diseases and “personalized” medicine. Drawing on the results of a qualitative study of 34 key Canadian stakeholders (including drug regulators, funders, scientists, policy experts, pharmaceutical industry representatives, and patient advocates), we explore the major trends that are reportedly contributing to the growing interest of the pharmaceutical industry in niche markets. Informed by both these key informant interviews and a review of the relevant literature, our paper provides a critical analysis of the many different—and sometimes conflicting—views on the reasons for and extent of the shift toward niche markets. We consider some of the potential advantages to industry, as well the important implications and risks that arise from the increasing pursuit of niche markets and pharmacogenomics. While there are many potential benefits associated with targeted therapies and drug development for historically neglected rare diseases, niche market therapies also present evidentiary challenges (e.g., smaller clinical trials and enrichment strategies) that can make approval decisions difficult, and uncertainties remain around the true benefits of many therapies.

KEY WORDS: pharmaceutical policy, niche markets, pharmacogenomics

Introduction

In recent years, a wide range of studies and reports in the literature and news media have raised the issue of an apparent innovation crisis in the pharmaceutical sector (Garnier, 2008; Light & Lexchin, 2012). According to some sources, while research and investment in pharmaceutical development has nearly doubled in recent decades, there has been no corresponding increase in the discovery of new chemical entities (Woodcock, 2007). Others point to escalating drug development costs (DiMasi & Grabowski, 2007), declining new drug approvals (Hait, 2011), and an increasingly stringent regulatory environment (Avery, 2010). Concurrently, reports abound about the death, or at least the decline, of the blockbuster model of drug development (Collier, 2011)—where large, brand-name pharmaceutical companies rely on a portfolio of drugs that gross more than U.S. $1 billion per year—which has dominated the pharmaceutical sector for decades.
Faced with new challenges and an evolving drug development environment, many pharmaceutical companies are now shifting development strategies (Policy Experts 1 and 5; IP Expert 1) and considering “new directions to maintain growth and stability” (Evans, 2010, p. 97). In recent years, one widely observed shift has been that “pharmaceutical R&D has slowed and has tended to concentrate on smaller markets such as conditions affecting fewer people or drugs tailored to meet an individual’s needs” (UK Parliamentary Office of Science & Technology, 2010, p. 1). While the pharmaceutical industry has traditionally shied away from smaller drug markets due to the revenue limitations presented by the reduced patient base (Woodcock, 2007), many major pharmaceutical companies are now aggressively pursuing the rare disease market (Dolgin, 2010). According to the U.S. Food and Drug Administration (FDA), nearly 200 drugs for the treatment of rare diseases enter development every year and further, about one third of new drug approvals are used in the treatment of rare diseases (Rockoff, 2013).

At the same time, rapid advances in genomic technologies have improved our understanding of how genes and genetic variation contribute to drug response, which has spurred the trend toward “personalized medicine.” Advances in the field of pharmacogenomics, the study of the influence that genetic factors play in drug response (National Human Genome Research Institute, 2014), may eventually allow physicians to routinely use an individual’s genetic information to guide drug treatment decisions (National Human Genome Research Institute, 2014). More and more pharmaceutical companies are now pairing drug products with companion diagnostics that can stratify populations based on an individual’s genetic predisposition to respond to drug treatments (Collier, 2011). Pharmacogenomics contributes to the establishment of niche markets by targeting patient subsets with particular genetic biomarkers, thereby stratifying broader disease categories into rarer disease genotypes.1 Some have even suggested that pharmacogenomics may help to jump start drug development pipelines by identifying new targets for treatment and improving the success of drug development (Hogarth et al., 2006, p. 11).

The number of pharmacogenomic products on the U.S. market has increased steadily from only a handful in 2001 to several dozen in 2011 (Cohen, 2012), but this trend may be accelerating. According to the Personalized Medicine Coalition (2014), more and more products in clinical development rely on a clinical biomarker: 30 percent of all treatments in late clinical development, 50 percent of all treatments in early clinical development, and 60 percent of all treatments in pre-clinical development. Researchers now increasingly consider whether existing drugs, or those under development, are broadly applicable to all patients, or whether they are most effective in a particular subset of patients (Pharmaceutical Representative 2).

The potential profitability of niche market therapies is well demonstrated by the number of these drugs that have already achieved blockbuster status. Thomson Reuters reports that drugs for the treatment of rare or “orphan” diseases now account for an increasing proportion of blockbuster drugs: of the 86 orphan drugs included in a 2012 study by Thomson Reuters, 25 (or 29 percent)
generated more than U.S. $1 billion in annual revenue—exactly the same proportion of non-orphan drugs in the study (83 out of 291, or 29 percent) that were considered to be blockbusters (Thomson Reuters, 2012, p. 10). The growing number of niche market products achieving massive revenues has led to the coining of the term “niche-buster” model (Collier, 2011). A couple of pharmacogenomic drugs, as well, have already achieved blockbuster status: Herceptin (trastuzumab) with an estimated U.S. $6.08 billion in sales (FiercePharma, 2012) and Gleevec (imatinib) with U.S. $4.7 billion (Pollack, 2013) in sales in 2012.

This paper explores many of the trends that are reportedly contributing to the growing interest of the pharmaceutical industry in niche markets in general, and pharmacogenomics in particular. Drawing on interviews with key Canadian informants and a review of relevant literature and media reports, this paper explores both the driving forces behind the shift and the attendant risks and benefits. We take a closer look at some of the potential advantages to industry in these markets, but also illustrate some of the important implications and risks that arise from the increasing pursuit of niche markets and pharmacogenomics. The pharmaceutical industry typically highlights the advantages for patients of targeting drug therapies and of addressing unmet medical need in smaller patient populations. But it is also clear that industry has a significant interest in capitalizing on new opportunities for profit in these niche markets, which raises potential policy and ethical concerns.

Methods

To capture and construct a multidimensional representation of the opportunities and concerns raised by pharmacogenomic-based drug development, including the ethical, legal, and social issues involved, we undertook a qualitative, expert interview-based study that combined interviews with key Canadian informants with a review of relevant literature and media sources. Expert interviews are a form of semi-structured interviews where the experts are deliberately selected (Muskat, Blackman, & Muskat, 2012). The objective of the study was to provide insight into the regulatory and policy responses that may be necessary to both harness the benefits of pharmacogenomics and mitigate the risks and uncertainties presented by these new technologies.

Expert informants were selected based on having a high level of experience or knowledge around pharmacogenomic research, pharmaceutical development, health ethics and/or health care policy, and decision making. Participants were purposefully selected from across a wide range of stakeholder groups in order to construct a broader account of the perceived legal, ethical, and social implications of pharmacogenomic drug development. Clinical researchers, scientists, and policy experts were selected through a search of authors who had published in peer-reviewed journals and/or who held key positions at academic institutions or government organizations. Stakeholders working in the area of regulation, funding, and health technology assessment were recruited through contacts at key public agencies including Health Canada and provincial ministries of health,
or based on public profiles posted on agency websites. Pharmaceutical industry representatives were primarily identified through the assistance of stakeholder organizations, namely Canada’s Research-Based Pharmaceutical Companies. Similarly, patient advocates were recruited with the assistance of several patient advocacy networks. Other industry representatives were recruited with the assistance of the Centre for Innovation Law and Policy at the University of Toronto. Intellectual property law experts were identified through contacts in the legal community and from the websites of law firms specializing in intellectual property law in the biotech sector. Additional key informants were recruited through snowball sampling (i.e., based on the recommendation of other key informants).

Interviews ranged from 30 to 90 minutes in length, with an average duration of approximately 1 hour. The majority of interview participants were located in Ontario and these interviews were largely conducted in person at the participant’s workplace. A few participants were located in other Canadian provinces and these interviews were conducted by phone. All interviews were conducted in English. Five different individuals were involved in interviewing participants, but interviews were consistently conducted by one of two dedicated researcher coordinators (Gibson and Raziee). With permission, all interviews were recorded and transcribed.

We used a semi-structured interview guide with common questions for all interviewees and additional specific questions targeting the expertise of particular stakeholder groups. All questions were open-ended to allow participants to elaborate on particular topics they felt to be important. Interview questions touched on a range of topics including general perceptions around growing interest in pharmacogenomics and niche markets, issues in clinical development, regulatory challenges in the pharmacogenomic context, and challenges in access and reimbursement. The results reported in this paper are drawn primarily from the first two topic areas: general perceptions around growing interest in pharmacogenomics and niche markets and issues in clinical development. The major questions in these two topic areas asked of all interview participants were:

- Many sources report that there has been a movement in the pharmaceutical sector away from the “blockbuster” model of drug development toward niche market development. Do you think this is an accurate description of a major trend in the pharmaceutical sector? What are the reasons for and implications of such a shift?

- How does the pharmacogenomic context impact on clinical development? What advantages or challenges does it present?

- Pharmacogenomics employs inclusion and exclusion criteria based on genetic markers. Under what circumstances is excluding marker-negative patients justified? What level of evidence is necessary to justify including or excluding patients?
How do you balance the need for robust evidence on the safety and efficacy of a drug product with the desire to get a promising therapy to market quickly?

The analysis of the interview responses involved a modified thematic analysis approach based on grounded theory techniques: transcripts were read and then fractured by identifying sections of data that related to a theme, idea, or concept (i.e., codes) and similar codes were organized into overarching themes. Data analysis proceeded concurrently with data collection to allow for constant comparison of emerging concepts and for new concepts relevant to the study objectives to be explored through subsequent interviews.

The various ethical, legal, and social issues raised during interviews also helped establish a framework to guide further research based on a review of relevant literature and media sources. The literature review was conducted concurrently with the analysis of the interview responses to allow for ongoing comparison of themes and ideas identified through interviews and in the literature. The literature search was primarily conducted using Google Scholar, Scopus, Web of Science, and PubMed in order to locate peer-reviewed articles across many disciplines and sources. Additional sources were located through drilling down to sources cited in the initial peer-reviewed articles. Media sources were primarily located through a standard Google search. The initial stage of the review involved more general searches, such as around broader themes of the challenges of clinical development in the pharmacogenomic context, and then became more targeted as more specific points and concerns were identified through the analysis of interviews. The goal of the review was to provide background for issues discussed by participants; to help validate different perspectives raised during interviews; or to further explore certain questions, concerns, or suggestions raised during the study.

The identities and affiliations of all interview participants were kept confidential so that they would be comfortable expressing their true opinions. Any other information from interview responses that might be used to identify individual participants has been omitted from this paper. This study received research ethics approval from the University of Toronto Research Ethics Board.

Limitations and Bias

While interviewing a wide range of stakeholder groups was useful for representing a broad range of perspectives, one drawback was that the different groups often varied considerably in their knowledge and experience around pharmacogenomic-based drug development. For example, while interviewing scientists, the discussion would often focus on the more technical elements of clinical development, whereas other groups, such as patient advocates or intellectual property experts, often had only limited knowledge of issues around clinical development. This impacted the questions answered, the level of detail provided, and the flow of the discussion—all of which reduced the overlap on
points covered. The open-ended nature of the questions further broadened the scope of the topics discussed during interviews. As a result, during data analysis, it was often difficult to identify areas of consensus or disagreement on particular topics between more than a few interview participants.

There was some unevenness in the number of participants from each stakeholder group; while some stakeholder groups were represented by 5–7 informants, others were only represented by 2–3 informants. However, as discussed below, many participants had knowledge in multiple disciplines, so there was significant overlap in the expertise of many of the stakeholder groups. The sample size within any one stakeholder group was too small to draw any broad conclusions about the perspectives of a particular group on pharmacogenomic drug development. A more in-depth study with a larger sample size within specific stakeholder group would cast more light on the opinions and experiences of particular groups and may warrant further research. The value of this study lies primarily with the insight it provides into the legal, ethical, social, and developmental challenges of pharmacogenomics as identified by a broad group of stakeholders.

As noted above, the study targeted Canadian informants. Some areas of questioning elicited answers that were specific to the Canadian context, namely questions around regulatory challenges and access and reimbursement. However, the responses around the trend toward niche markets and issues in clinical development—which are the focus of this paper—were much more universal. Further, during the literature review, publications were sought from across jurisdictions, which further reinforced the commonality of many of the perspectives expressed on these topics.

Results

This study brings forward the varying perspectives of key informants on different aspects of pharmacogenomic drug development. A total of 34 interviews were conducted between November 2011 and February 2013: five with clinical researchers and scientists, two with drug funders, three with health technology assessors, four with patient advocates, two with intellectual property law experts (lawyers), five with pharmaceutical industry representatives (three from brand-name companies and two from generic companies), six with drug regulators, and seven with policy experts on various aspects of health policy, bioethics, health economics, and pharmaceutical regulation. Throughout the paper, interview participants are referred to under the following categories: Scientist, Policy Expert, Drug Funder, Regulator, Health Technology Assessor, Patient Advocate, IP Expert, and Pharmaceutical Representative. Although some stakeholders interviewed had expertise in multiple areas, participants have been categorized according to their dominant role or area of expertise.

Throughout this paper, the opinions and perspectives of individual participants are identified only by the stakeholder group and a numerical code. Where
multiple stakeholders, whether within the same stakeholder group or across multiple groups, are listed in reference to a particular point, this was representative of multiple stakeholders who made a specific point or who shared a particular concern. Where the same point or concern was also referenced in the literature, the article citation is included alongside the stakeholder reference to indicate that the point was reflected both in interviews and in the literature review.

Pharmacogenomic drug development raises a host of unique ethical, legal, and social issues. Many of these issues arise from the multifaceted nature of this new development paradigm, which exists at the intersection of several important research and development contexts, perhaps most notably pharmaceutical development, diagnostic test development, and the development of treatments for rare diseases and serious or life-threatening conditions—all of which contribute to the opportunities and challenges encountered in pharmacogenomic drug development.

The first section of the discussion considers how the evolving drug development environment is pushing industry toward niche markets. The inefficiency of conventional drug development is often cited as part of the rationale for the shift toward targeted drug development: in the face of declining productivity, pharmacogenomics may offer the potential to lower or control costs by improving the clinical development success rate (Health Technology Assessor 3; Woodcock, 2007). Concurrently, as traditional disease markets have become increasingly saturated with multiple drug products and profits in these markets have been eroded by generic competition, industry has shown growing interest in untapped niche markets. Further, regulatory initiatives such as orphan drug policies have incentivized research into rare diseases by increasing the financial viability of these markets. But perhaps most significantly, the ability to charge a significant price premium for niche market products can make niche market products very profitable despite the more limited patient populations.

Niche market therapies present a number of evidentiary challenges that make approval and coverage decisions particularly difficult, and a number of uncertainties remain around the true benefits of pharmacogenomic therapies in particular. While interview participants commented on a wide range of factors that impact on clinical development strategies, the two aspects that garnered the most attention were first, the impact of pharmacogenomics on the quality of evidence developed during clinical trials, and second, the role of genetic biomarkers in enriched clinical trial designs. Both of these factors can have a significant impact on inclusion and exclusion criteria for clinical trials and on the quality and generalizability of the resulting evidence. The final part of the discussion thus explores the benefits and risks of smaller, more targeted clinical trials and enriched trial design and potential strategies for minimizing the evidentiary challenges often associated with pharmacogenomic drug development.
Discussion

The Dynamics of Niche Markets

A More Efficient Approach to Development? According to industry sources, gaining approval for a new drug product takes an average of 10–15 years of research and development and costs more than U.S. $1.2 billion (Pharmaceutical Research and Manufacturers of America, 2013). Put another way, products developed under the traditional drug development model would have to show the potential for at least $500 million per year in sales to cover development costs (Trusheim et al., 2007). More than 80 percent of drugs that enter clinical development never reach the market (Shah, 2006). One interviewee referred to the fact that the high cost of conventional drug development results from this high attrition rate (Scientist 5). According to one estimate, an average of 39 percent of drug development costs go into failed drugs (Keeling, 2007).

Pharmacogenomics has received particular attention in oncology research. Cancer drug development is regarded to be a particularly slow, risky, and expensive process, with a failure rate for preliminary products that has been reported to be more than 90 percent (Kelloff & Sigman, 2012). On average, a higher percentage of cancer drugs fail after reaching late-stage clinical testing in comparison to other categories of drugs and this high rate of drug attrition can increase development costs (DiMasi & Grabowski, 2007). Targeted development strategies are often regarded as a means to potentially shorten development time and lead to significant cost savings.

Under the right conditions, pharmacogenomics may offer significant potential for increasing the productivity and success of drug development (Hogarth et al., 2006). Three of our interviewees pointed out, in line with what some commentators have argued (Cohen, 2012), that a reliable clinical biomarker can help “enrich” clinical studies for populations with better responses (discussed in more detail below), which may reduce the size and timeframe, and consequently the cost, of clinical trials and streamline regulatory reviews (Policy Expert 1, Regulator 3, Health Technology Assessor 3). Several interviewees suggested that by identifying the patients for whom the drug is most likely be safe and effective, pharmacogenomics may help the drug pass approval hurdles and move more rapidly to the market (Policy Expert 1, Regulators 3 and 4, Pharmaceutical Representative 2; Shah, 2006). Commentators in the literature have also pointed out that this may translate into longer effective patent life (Trusheim et al., 2007). One interviewee suggested that the ability to exclude patients who are more likely to suffer an adverse event may reduce drug companies’ potential liability to trial participants (Policy Expert 2). Pharmacogenomics may also contribute to faster market uptake where a diagnostic test can effectively identify those patients most likely to respond to treatment, leading to better clinical performance within the targeted population (Cohen, 2012; Trusheim et al., 2007).

On the other hand, some question the veracity of the research and development costs commonly reported by industry (Regulator 3; Light & Lexchin,
2012; Light & Warburton, 2011). Light and Lexchin (2012, p. 2) note that “[a]lthough the pharmaceutical industry emphasizes how much money it devotes to discovering new drugs, little of that money actually goes into basic research.” Some suggest that drug companies often inflate the costs of clinical trials, exaggerate the time frame of research and development, and overestimate corporate research (Light & Warburton, 2011). Light and Warburton (2011) argue that most significantly, about half of estimated research and development costs consist of the “cost of capital”—that is, how much profit the company would have made if they had invested in an index fund rather than investing in research and development. If actual drug development costs have indeed been significantly inflated, this raises questions about whether the extremely high prices demanded for many niche market therapies truly reflect development costs.

Along the same lines, some interviewees expressed scepticism about the efficiencies to be gained from pharmacogenomic drug development. One scientist pointed out that where a biomarker is poorly correlated with drug response, targeting strategies are unlikely to improve efficiency—and indeed may even be less efficient than non targeted clinical trials (Scientist 4). Other interviewees (Policy Expert 5, Pharmaceutical Representative 3) and commentators (Trusheim et al., 2007) further point out that there are also additional costs involved in collecting genetic information, analyzing pharmacogenomic data, and developing a companion diagnostic test. One scientist indicated that a flaw in preclinical information may negate many of the potential efficiencies to be gained from the targeted approach to drug development (Scientist 3). This is in line with Avery’s (2010) argument, for example, that generating pharmacogenomic data actually ends up being more expensive due to the additional costs involved in gathering and analyzing pharmacogenomic data, developing companion tests, and redesigning trials or adding more studies. Some companies remain hesitant about investing in pharmacogenomics due to uncertainty around how current intellectual property and regulatory regimes apply to the pharmacogenomic context (Keeling, 2007). While targeted drug development may eventually lead to cost savings in the future, for now, pharmacogenomic drug development may, in many cases, actually be more expensive than conventional drug development (Pharmaceutical Representative 1).

From Saturated Markets to Untapped Markets

In recent decades, the brand-name pharmaceutical sector has often devoted more research and development resources toward drugs for conditions for which treatment options currently exist, or toward conducting new trials for existing drugs to gain approval for new indications and expand existing disease markets (Applbaum, 2006). However, in line with discussion in the literature, a couple of interviewees suggested that the viability of this development strategy now appears to be waning as the flood of similar drug products has resulted in saturated markets with little room for additional blockbuster products (Policy Expert 5, Pharmaceutical Representative 2; Collier, 2011). Morgan and colleagues
note that while “the blockbuster markets of the 1990s were ideal for [follow-on competition] … by the early 2000s, the clinical and economic opportunities for such competition had declined considerably” (Morgan, Cunningham, & Law, 2012, p. e5580). Since many of the largest disease markets are already saturated with multiple drug products—for example, many common conditions such as diabetes and high blood pressure are already well-served by existing drugs (Policy Expert 5)—developers may simply be driven toward untapped niche markets where there is little or no competition from me-too drugs or generic products (Boon & Moors, 2008).

There are also a number of practical benefits to pursuing untapped niche markets. In broad heterogeneous populations where multiple products already exist, it is often more difficult to demonstrate incremental benefit; in general, “as more effective drugs reach the market, the hurdle for developing even better ‘follow-ons’ becomes higher” (Hait, 2011, p. 384). In contrast, in a smaller, narrowly defined population that is specifically targeted by the therapy, it may, according to one interviewee from the pharmaceutical industry, be easier to demonstrate incremental benefit (Pharmaceutical Representative 2). In this vein, some interview participants expressed concern that new niche market therapies commonly lead to only very marginal health improvements (Regulators 3 and 4); where there are few or no treatment options available for the particular subset of patients targeted by the drug, even very marginal health improvements may be sufficient to justify drug approval, and subsequently funding coverage. Further, two interviewees suggested that disease stratification may create monopolistic markets without any competition to drive down prices (Regulators 2 and 3). This argument has also been made in the literature (Boon & Moors, 2008). Consequently, drug companies may be able to drastically cut their marketing costs because there is little or no competition within niche markets and therefore no need to create brand preference—market share is already guaranteed (Regulators 2 and 3). Instead, “marketing” initiatives can focus more on expanding patient access and increasing reimbursement by drug funders—for example, through lobbying and supporting patient advocacy groups that push for broader access to drugs.

According to two regulators, the pharmaceutical industry has conventionally preferred chronic diseases with a large population base since such markets generate reliable long-term sales potential (Regulators 2 and 3). However, some niche markets also offer the opportunity for long-term sales potential, albeit in smaller populations but with significantly higher unit prices. As Simoens (2011, p. 2) notes, disease stratification may create “a monopolistic market where chronically ill patients receive long-term treatment with [an] orphan drug…. For example, many oncology drugs that have been developed recently or that are in the pipeline treat cancer essentially as a chronic condition; rather than curing cancer, they suppress or slow tumor growth for as long as the patient takes the drug (Scientist 5 and Patient Advocate 1). One scientist offered the example of the pharmacogenomic drug Gleevec: some patients have stayed alive on Gleevec for more than a decade, but treatment requires that the patient essentially remains on the drug for life (Scientist 5). The huge financial success of Gleevec is likely
driven in large part by the fact that patients often take this highly expensive drug over the long term. This scientist also noted that some targeted therapies such as Herceptin are even being promoted for preventative treatment (Scientist 5), which represents another opportunity for expanding markets and promoting long-term sales of the drug.

**Incentivizing Research into Orphan Diseases**

As noted above, the modern drug development process has long been regarded as slow, inefficient, and expensive (Hait, 2011; Keeling, 2007). Two interviewees noted that the pharmaceutical industry often argues that the extremely high cost and long development timelines for getting new drug products to market requires a system to incentivize pharmaceutical innovation (Regulator 2, Drug Funder 1). The substantial increase in the development of drugs for rare diseases over the past three decades is often directly attributed to legislative initiatives that have incentivized drug development related to orphan diseases (Coté, Xu, & Pariser, 2010).

In 1983, the U.S. government passed the Orphan Drug Act (ODA), which offers a special designation to drugs that treat a rare disease—defined as a disease affecting less than 1 in 200,000 people in the United States—and provides a number of incentives including tax benefits on clinical trials, fast-track approval, grants, and 7 years of market exclusivity (Coté et al., 2010). In 2000, a similar model was introduced in Europe when the European Commission passed regulation 141/2000 implementing a number of incentives for the development of drugs for the treatment of a “life threatening, seriously debilitating, or serious and chronic condition” that affects less than 5 in 10,000 people in Europe (Committee for Orphan Medicinal Products and the European Medicines Agency Scientific Secretariat, 2011). Incentives provided after designation by the European Medicines Agency (EMA) include fast-track approval, funding for pre-clinical and clinical studies, and up to 10 years of market exclusivity, as well as other incentives such as a government grants that vary by member country.

Orphan drug policies may also incentivize pharmacogenomic research if the targeted population is small enough to meet the applicable definition of an orphan disease. Indeed, several pharmacogenomic drugs have already qualified for orphan drug status in both the United States and Europe (Koch, 2012). In some cases, there may be a legitimate need to incentivize pharmacogenomic research if stratification based on genetic features results in some patient groups being so small that developing specific medicines targeting these groups could be prohibitively expensive (Nuffield Council on Bioethics, 2003). Consequently, incentives may be necessary to encourage industry to develop medicines for these narrow populations.

Significantly, a single drug may be eligible for multiple orphan designations if it targets multiple distinct niche markets, which may allow sponsors to maximize the sales potential for existing drugs by obtaining additional rare disease designations (Orphan Drug Regulations, 2013, p. 35120). Several interview
participants noted the potential for pharmacogenomics to break up a common
disease into multiple “orphan” conditions (Policy Expert 1, Regulator 3, Health
Technology Assessor 2, Pharmaceutical Representative 1): they hinted at the fact
that if you stratify patient populations enough based on genetic profiling, any
disease may become an “orphan disease.” This concern has also been raised in
the literature. Loughnot (2005), for example, cautions that orphan drug legislation
could be misused though “high-tech salami slicing” of diseases into multiple
“orphan genotypes” for the primary purpose of qualifying for orphan drug
status, and thus reaping the accompanying financial benefits. The Nuffield
Council on Bioethics (2003) has also cautioned about this possibility of the
“reclassification of diseases” to artificially increase niche markets. As stated by
Herder (2013, p. 244), “new insights from genomics and epigenomics are
rendering the boundary between common and rare disease increasingly mutable,
potentially exploding the scope of legislated definition of orphan disease.”

Charging a Price Premium

For the pharmaceutical industry, likely one of the most important incentives
for pursing niche markets is the extremely high prices that can be charged for
many of these products (Regulators 2 and 3; Trusheim et al., 2007). As several
interviewees emphasized, drug companies typically justify the very high cost of
niche market products by arguing that they must recoup their development costs
across a smaller patient population (Health Technology Assessor 1, Regulator 3,
Drug Funder 1). One informant also noted that industry often argues that a
higher price for a limited population is justified if patients derive a greater benefit
(Policy Expert 1).

The development of drug products for niche markets is important, particular-
ly given the historical neglect of rare disease markets and the resulting high level
of unmet medical need. Many niche market therapies target serious or life-
threatening diseases, most notably cancer: close to half of successful pharmacoge-
nomic therapies are used in the treatment of cancer (Cohen, 2012, p. 752)—likely
due in part to the high prevalence of the disease and the fact that cancer appears
easily stratifiable based on the type of mutation (Scientist 5, Health Technology
Assessor 2). Moreover, about one third of drugs granted orphan designations in
the United States are used in the treatment of cancer (Wellman-Labadie & Zhou,
2010).

More and more drug companies are beginning to appreciate the reputational
goodwill and bargaining power that can be gained by developing products that
address unmet medical need and critical illness (Herder, 2013). Several inform-
ants noted the tough political dimension that rarity adds to decision-making:
where there are few or no treatment options available for a condition, and
particularly where the condition is life-threatening, regulators and funders often
face intense pressure to provide access to new therapies even in the face of
uncertain evidence or evidence of only marginal treatment benefit (Regulators 2
and 3, Health Technology Assessor 2). One health technology assessor noted that
drug companies may use the “political economy of rarity” to justify the very high prices of new targeted therapies (Health Technology Assessor 2). Similarly, one patient advocate repeated the concern around pharmaceutical companies developing products for “rare” diseases and then “effectively holding payers ransom” in demanding extremely high prices for the drugs (Patient Advocate 1). Further, the smaller the market, the more identifiable are the target patients, which can increase public pressure to fund, as two regulators pointed out (Regulators 2 and 3).

Some interviewees suggested that at first glance, it seems that the rarity of the diseases treated by expensive niche market therapies may serve to limit the cost implications for drug funders (Policy Expert 1, Pharmaceutical Representative 1). However, one drug funder indicated that it can be very difficult to estimate the actual size of the patient population that may receive the drug (Drug Funder 1). It is common, in all areas of pharmaceutical development, for manufacturers to seek initial approval for a particular indication or population and then subsequently expand the market by seeking approval for additional indications or patient groups—pharmacogenomics is no different (Pharmaceutical Representative 2). One policy expert pointed out that off-label drug use—use of a drug for indications or populations that have not been approved by regulatory authorities—can also expand the market for expensive niche market products (Policy Expert 1). A couple of interview participants expressed the concern that as a pricing strategy, drug manufacturers might seek a high price on the basis of the initially approved niche indication, and then strive to maintain the same price even as the market base expands, either through off-label use or through new approved indications or patient groups (Policy Experts 1 and 3).

The move toward niche markets was viewed by several policy experts as concentrating energies and resources on a certain group of diseases, and further, toward certain subpopulations within particular disease categories—and at a very high cost at the individual level (Policy Experts 1, 3, and 4). The high cost of many new niche therapies was a fundamental source of tension discussed by participants during interviews. Several informants commented on the need for drug manufacturers to consider what health-care budgets can afford to pay for pharmacogenomic drugs (Regulator 2, Drug Funder 1, Policy Expert 5). A few interviewees noted that from a strategic perspective, industry must be realistic about how profitable a drug can be if public and private insurers are unwilling to pay the steep prices demanded (Regulators 2 and 3, Policy Expert 5).

Concern around the extremely high prices demanded for niche market products is also widely reflected in the literature. As an illustration, in 2013, more than 100 influential cancer specialists from around the world criticized the often extreme and unsustainable prices demanded by industry for new cancer therapies and called for a reduction in prices (Experts in Chronic Myeloid Leukemia, 2013). The article noted that eleven out of 12 cancer drugs approved by the FDA in 2012 were priced at over U.S. $100,000 per year. Even more disturbing was the fact that the price of some cancer drugs has, in fact, increased substantially since market entry. For example, when the pharmacogenomic drug Gleevec entered the U.S. market in 2001, the drug cost U.S. $30,000 per year, but its price has now more than tripled (Experts in Chronic Myeloid Leukemia, 2013).
Understanding the Evidentiary Challenges

**Small Clinical Trials.** One regulator pointed out that the size of studies is an important consideration in the design of all clinical trials (Regulator 6). Along with another regulator, this informant noted that in general, while interventions with marginal effectiveness require larger-scale clinical trials, where a drug is more effective, its efficacy may be demonstrated in smaller-scale clinical trials (Regulators 2 and 6). Other interviewees pointed out that as new drug treatments are usually associated with modest improvements compared to standard treatments, clinical trials typically require large numbers of patients (Regulator 3, Health Technology Assessor 2). Indeed, a couple of informants noted that the pharmaceutical industry has become accustomed to conducting large-scale clinical trials because they are necessary to demonstrate the small size effects (i.e., marginal benefit) that are typical of most new drug products (Regulator 3, Health Technology Assessor 2).

Several interviewees confirmed that as interest in niche market therapies has increased, so too has the trend toward smaller, more targeted clinical trials (Policy Expert 1, Regulators 1 and 3, Scientist 5). This seems logical, as there are often an inherently limited number of patients with the disease (Boon & Moors, 2008). In the pharmacogenomic context, disease stratification introduces the reality of smaller patient populations, which may inherently limit the number of patients that meet the inclusion criteria for clinical trials (Policy Experts 1 and 5). As noted by Owen and colleagues (2008, p. 236), "[o]rphan drugs, and innovative specialized drugs used in relatively small populations, encounter a disadvantage compared with more widely used drugs, as large-scale clinical trial data are usually unavailable." Consequently, drugs for niche markets may be approved on the basis of safety and efficacy data that may not be as robust as that produced in larger-scale clinical trials.

From an efficiency perspective, there are some potential advantages to reducing the size of clinical trials. Smaller trials may be quicker to conduct with regard to patient enrollment, reviewing patient records, or collecting and testing blood and tissue samples (Hackshaw, 2008). Smaller trials may often be conducted across fewer centers, making the process of obtaining ethics and institutional approval comparatively simpler (Hackshaw, 2008). However, as one interviewee pointed out, where a biomarker is rare, it may take longer to identify potential study participants (Pharmaceutical Representative 2). In the pharmacogenomic context, a genetic biomarker can be used to limit the study to the population with the highest possibility of showing response—a strategy known as enrichment, discussed in more detail in the next section—which allows drug efficacy to be demonstrated across a smaller sample of patients (Regulators 3 and 4, Scientist 5).

Several interviewees, on the other hand, pointed out that smaller clinical trial size raises questions about the quality of the resulting evidence (Policy Expert 1; Regulators 1, 3, and 5). Yet, an interviewee from the pharmaceutical industry noted that in a well-designed targeted clinical trial, a smaller sample size should
not compromise the ability of the trial to measure the efficacy of the drug (Pharmaceutical Representative 2). Concerns over the impact of a small sample size thus vary depending on the strength of the association between the biomarker and drug response. According to another interviewee from the pharmaceutical industry, some of the most significant concerns about smaller clinical trials are directed not at the ability of the study to capture drug efficacy, but rather at their reduced ability to detect potential safety issues (Pharmaceutical Representative 3). A general concern with clinical trials of all sizes is that they primarily detect common and frequently occurring adverse drug reactions; rare or long-term side effects may only become apparent after the drug has hit the market and is prescribed to a large number of patients (Suvarna, 2010). These concerns are exacerbated when the size of the trial is reduced since a smaller sample size lowers the probability of detecting less common adverse events (Pharmaceutical Representative 3). The result is that clinical trials may be able to identify responders quite effectively, but uncertainty remains around the safety profile of the drug (Pharmaceutical Representative 3). This may, according to two interviewees from industry, create a false improvement in the benefit/risk profile (Pharmaceutical Representatives 1 and 2). Random sampling errors caused by small patient sample sizes can also contribute to false positive and false negative conclusions (Pharmaceutical Representative 2), as well as overestimation of the magnitude of an association between a treatment and an outcome (Hackshaw, 2008). Smaller sample sizes can also make it difficult for investigators to adjust for the myriad confounding factors found in pharmacogenomics (Pharmaceutical Representative 3; Hackshaw, 2008).

As noted above, the exigencies and evidentiary uncertainties in niche markets can skew the dynamics of decisionmaking around niche market products. Given that many pharmacogenomic products are used in the treatment of serious or life-threatening diseases with few or no alternative treatment options, regulators are arguably more likely to be flexible with regard to the safety and efficacy evidence required for market approval (Herder, 2013). The concern, as expressed by one health technology assessor, is that when a treatment is targeted to a very specific subset of patients and the size of trials inevitably decreases, drug manufacturers may simply argue that regulators will have to cope with greater uncertainty inherent in smaller clinical trials (Health Technology Assessor 2). This informant further noted that the public sympathy that can be gained from the image of a critically ill patient being denied access to the only available treatment can become a powerful bargaining chip that industry may use to sway the interpretation of regulatory standards in their favor—including toward lowering the evidentiary bar for clinical trial results (Health Technology Assessor 2).

Overall, there is a balance to be struck between addressing the reality that rare diseases affect small populations while still meeting standards of scientific rigor. Like any risk, the impacts of a smaller sample size need to be properly assessed and managed. Some argue that given the level of unmet medical need for many rare diseases, the smaller sample size itself should not be used as an excuse for not running the trial at all (Pharmaceutical Representative 2). Many
interviewees emphasized that some concerns over smaller clinical trials may be addressed through proper statistical methods and scientific validation (Policy Experts 2 and 5; Regulators 1, 2, and 6; Scientist 3). However, proper methods for designing, analyzing, and statistically validating small biomarker-based clinical trials are still evolving (Regulator 1). Moreover, where niche market therapies are approved on the basis of a more limited level of evidence from small-scale clinical trials, as discussed in more detail below, it becomes more imperative to assess the benefits and risks of these drugs through the ongoing collection and analysis of data after market entry.

**Enrichment Strategies**

Double-blinded randomized clinical trials (RCTs) have conventionally been considered as the gold standard for detecting the effects of an experimental treatment (Frueh, 2009). In these trials, the drug is typically given to all comers, with little consideration for individual patient characteristics or circumstances that may impact on drug response (Scientist 3). While the traditional RCT design focuses on determining average treatment effect of a drug in a largely homogeneous patient population, pharmacogenomics is predicated on genetic heterogeneity within a patient population. Consequently, traditional RCTs may not accurately represent the benefit of pharmacogenomic products (Frueh, 2009).

A traditional RCT can mask treatment efficacy in a patient subgroup by including other subgroups for which the treatment has poor efficacy. Therefore, researchers are now using predictive biomarkers to prospectively select patient subpopulations that are more likely to respond to a given treatment so that detection of a treatment effect is more likely (U.S. Food and Drug Administration 2012)—a practice referred to as enrichment of the study population. Several interviewees pointed out that employing enrichment strategies is neither new nor limited to pharmacogenomic studies (Regulators 3, 4, and 5). Pharmacogenomics simply incorporates more technical or complex genetic biomarkers that researchers believe, based on a hypothesis, can help refine the population to increase efficacy and decrease adverse events (Regulator 4, Policy Expert 5). In the basic enriched clinical trial, the predictive biomarker of interest is evaluated on all patients. Patients in the marker-positive (M+) group are then randomized between treatments. Patients in the marker-negative (M-) group are excluded from further study under the rationale that only M+ patients will benefit from the experimental treatment. As a result, the only possible hypothesis concerns treatment effect within the M+ patient group (Simon, 2008). In line with commentators (Simon, 2008), several of our interviewees thought that an enriched design is generally appropriate in situations where investigators have a strong pre-existing biological or empirical basis for believing that M- patients will not benefit from the drug in question (Health Technology Assessor 1, Regulators 1 and 4, Scientist 4).

The primary reason for enrichment is study efficiency. First, the number of randomized patients required for an enriched clinical trial is comparatively fewer
than the number required for a traditional RCT since enrichment strategies may allow a more significant benefit to be demonstrated in a smaller population (Regulator 3, Health Technology Assessor 2; Simon, 2008). Enrichment may be viewed as a more rational approach to drug development that focuses more attention on determining which patients are the best candidates for each drug. Second, the enriched design’s increased sensitivity allows investigators to detect effects that may be impossible to detect with a traditional RCT (Kellogg & Markman, 2012). One pharmaceutical industry informant added that pharmacogenomics may potentially “rescue” drugs that have failed conventional all-comer clinical trials by defining a more appropriate patient population (Pharmaceutical Representative 2). Nevertheless, the efficiency of an enriched design will ultimately depend on variables such as the prevalence of M+ patients, the effectiveness of the treatment in M− patients, and the specificity of the companion diagnostic (Simon & Maitournam, 2004). Both the costs of conducting a clinical trial and the time required to bring the drug to market can potentially be reduced, conferring competitive and economic advantages to the manufacturer (Cook, Hunter, & Vernon, 2009). However, efficiency gains may be offset by the complexities that biomarker identification and validation introduces into the drug development process.

The Ethics of Inclusion and Exclusion

Interviewees pointed out that there are complex ethical and scientific concerns with including or excluding participants in clinical trials based on their genetic markers (Health Technology Assessor 1, Regulator 5) and ongoing debate around what level of evidence is required to justify the exclusion of M− patients from clinical trials (Health Technology Assessor 1; Regulators 1, 4, and 5). This debate is, according to some commentators and interviewees, complicated by ongoing uncertainty around the significance and usefulness of many biomarkers in predicting drug response (Policy Expert 3; Regulators 1, 5, and 6; Drug Funder 2; Bossuyt, 2011).

In principle, where the evidence demonstrates a clear association between a given biomarker and drug response, one policy expert argued that it is both rational and ethically defensible to exclude certain patients based on biomarker status (Policy Expert 5). Importantly, as several interviewees pointed out, study enrichment offers the benefit of individualization, allowing the treatment to be directed toward patients that are most likely to benefit and sparing other patients, who would likely not benefit, from potential harm (Regulator 4, Pharmaceutical Representative 1 and Patient Advocate 1; U.S. Food and Drug Administration, 2012). It may be ethically problematic to include certain patients in a trial if they are unlikely to benefit, face a higher risk of adverse events, and may potentially miss opportunities to receive more appropriate treatment (Regulator 5, Scientist 3; Evans, 2006; Kelloff & Sigman, 2012).

At the same time, improper exclusion of M− patients can also be ethically problematic. The main drawback of enriched designs is that their results are not...
generalizable to patients outside of the tested population. Arguably, excluding genotypes from clinical trials without sufficient justifications can be unethical because these studies will not be informative about whether the results will be applicable to other genotypes (Regulators 1 and 5; Crolla, 2006; Taube et al., 2009). Moreover, if the drug is never tested outside of the biomarker group, then the research will never address the question of whether M⁻ patients could also potentially benefit from the drug (Health Technology Assessor 1; Regulators 1, 4, and 5; Crolla, 2006). The treatment may have some effectiveness in M⁻ patients because the drug has off-target effects or because of the imperfect sensitivity of the companion diagnostic (Simon, 2008). Accordingly, another important factor to consider is the availability of alternative treatment options, and more specifically, the safety and efficacy profile of these alternative treatments in comparison with the pharmacogenomic treatment under development. One health technology assessor suggested that even if a drug has a lower success rate outside of the M⁺ group, it may, nonetheless, be high enough to still justify offering the drug to M⁻ patients, particularly where alternative treatment options are poor (Health Technology Assessor 1).

Determining diagnostic cut-off points may also be complex. In many cases, genetic testing does not simply reveal the presence or absence of certain genes in a binary sense. In oncology, for example, while some types of mutations almost always show up in all the cells in a given tumor, other types of mutations may only be found in a subset of the tumor cells. This raises the issue, as pointed out by several interviewees, of where to set the cut-off points in determining whether or not a patient is M⁺ or M⁻ (Regulator 6, Scientist 5, Health Technology Assessor 2). Many patients may be in a gray zone where potential benefit can still be significant. Further contributing to the complexity of diagnostic testing is the fact that a particular genetic test may only detect one of the many ways in which a gene may be mutated (Scientist 5). Further, most diseases have multi-allelic genetic components, meaning that more than one genetic change is involved in pathogenesis or responsiveness (Regulators 1 and 5, Scientist 3). In oncology, for example, some genetic changes are drivers of cancer, while others are only bystanders with limited clinical significance (Kelloff & Sigman, 2012). Finally, genetics are only one part of the equation of a drug’s effectiveness and toxicity; environment factors, for example, often play a predominant role (Regulator 5; Hait, 2011).

**Improving the Evidence for Pharmacogenomic Products**

A few informants argued that it is not possible to properly assess the diagnostic validity of the predictive test without conducting clinical trials on both M⁺ and M⁻ patients (Health Technology Assessor 1, Regulators 4 and 5). Such comparisons typically require multi-arm clinical trials: testing the drug in M⁺ patients, in M⁻, and the control arm (Health Technology Assessor 1). On the other hand, multi-arm clinical trials are typically more complex, time-consuming, and expensive to conduct (Health Technology Assessor 1). As such, some
commentators have argued that if manufacturers are required to conduct multi-arm studies, conducting such studies will be too complex, onerous, and time consuming and may, in fact, prevent a useful drug from being developed (Maitland & Schilsky, 2011; Trusheim et al., 2007).

To help bridge this debate, there is growing interest in the possibility of designing pharmacogenomic clinical trials with “adaptive” features which enable prospectively planned modification in the design of the trial after patient enrollment (Regulator 1, Health Technology Assessor 3, Pharmaceutical Representative 2; van der Baan et al., 2012). These adaptive features are “changes in design or analyses guided by examination of the accumulated data at an interim point in the trial” that “may make the studies more efficient (e.g., shorter duration, fewer patients), more likely to demonstrate an effect of the drug if one exists, or more informative” (U.S. Food and Drug Administration, 2010, lines 36–40).

Van der Baan et al. (2012, p. 571) argue that adaptive enrichment strategies may be particularly useful in the pharmacogenomic context as “evidence may not be strong enough upfront to determine that a specific gene is indeed an effect modifier of the treatment effect.” This complicates decisions around whether patients with different biomarker status should be given the same treatment or dose. With an adaptive trial design, research may be able to learn about the effect of genetic variability on drug response throughout the course of the study and immediately apply this information to modify study design. Specifically, an adaptive trial design “provides the possibility to start the study with a whole patient population and, if indicated by differential treatment responses, to drop genetic subgroups during the trial, ending up with patient showing best treatment responses” (van der Baan et al., 2012, p. 577). A couple of informants noted the advantages of this approach: if the biomarker is found to have value, then the researchers may adopt a new study design and continue only with the M+ group; if the biomarker is not useful, then the original all-comer trial continues unchanged (Health Technology Assessor 3, Pharmaceutical Representative 2). However, van der Baan et al. (2012) caution that adaptive trials are more complex to conduct and analyze, and that adaptive enrichment may limit information on the excluded subgroups, and consequently, the inferences around safety and efficacy that can be made for these groups.

As with approval based on smaller clinical trials, the use of enrichment strategies heightens the need to continue to monitor the use of these drugs during the post-market phase. Enriched designs will inevitably become increasingly common as pharmacogenomics research continues to advance and as a corollary, strategies for maintaining data quality will also grow in importance. The FDA notes that when enrichment strategies are used, the “extent of data that should be available on the non-enriched subgroup should always be considered” and “post-market commitments or requirements may be requested to better define the full extent of a drug’s effect” (U.S. Food and Drug Administration, 2012, p. 32). If following the clinical trial new data emerges that suggests that M− patients may obtain some benefit from the drug, then there may be a need for follow-up studies to test this theory, as two scientists argued (Scientists 3 and 5).
Well-performed observational studies and retrospective meta-analyses of prior clinical trials can also shed light on issues related to individualization beyond M+ patients (Lesko & Schmidt, 2012).

**Recommendations and Conclusion**

The pharmaceutical sector is constantly evolving, and increasing interest in niche markets is only one of the many ways in which the sector is changing. While the strategic reasons behind the growing interest in niche market development are complex, the pharmaceutical industry is likely adapting out of a combination of both necessity and opportunity. While some factors such as the inefficiency of conventional drug development and the saturation of broader disease markets are pushing the pharmaceutical industry toward untapped niche markets, drug companies have also recognized the potential advantages of these markets, including the incentives available through orphan drug policies, and perhaps most importantly, the significant price premium that can be demanded. While the blockbuster model of drug development is not dead, the structure of this development model is certainly shifting and niche-market drugs—including pharmacogenomic therapies like Gleevec and Herceptin—now account for an increasingly large proportion of blockbuster products.

There is no question that pharmaceutical development is a complex, lengthy, and expensive process. However, there is uncertainty, and sometimes conflicting evidence, around the cost of pharmaceutical development in general, and the efficiencies to be gained from targeted drug development, in particular. At this point, there can be no broad generalizations about the efficiencies to be gained from pharmacogenomic-based drug development, and the reality may currently vary widely from case to case. Consideration should be given to how pharmacogenomics may impact the way that rare disease is defined, and consequently, how orphan drug policies are interpreted and applied. Nonetheless, as the science improves and targeted development becomes more established, the benefits—and challenges—of pharmacogenomic-based drug development will become more concrete, hopefully clearing away the haze of hype that currently obscures the field of “personalized medicine.”

A number of factors converge in the pharmacogenomic context to create a particularly charged decision-making environment. Pharmacogenomic drugs often treat serious or life-threatening diseases with few or no alternative treatment options, which can increase pressure on regulators and funders to provide early access to these drugs even in the face of uncertain safety, efficacy, and cost-effectiveness. Perhaps, the most controversial aspect of the shift toward niche markets is the extremely high prices that are often demanded for these products. The high price creates ethical challenges in making resource allocation decisions, particularly, since the financial impact of niche market therapies can be hard to predict because, *inter alia*, the potential for off-label prescribing can increase the number of patients who may receive the drug and some patients may take these drugs over the long term. As more and more niche market therapies hit

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the market, decisions around which drugs should be funded in the health-care system will become increasingly difficult and the pharmaceutical industry must be realistic about how the prices demanded will impact the sustainability of niche market development. Drug funders in many jurisdictions are now increasingly experimenting with reimbursement schemes that involve a “pay-for-performance” or “risk-sharing” element where reimbursement is adjusted based on the resulting health and economic outcomes. Such schemes may serve as a valuable tool to control health-care spending in this context (Gibson & Lemmens, 2014).

Pharmacogenomic drug development, while offering certain advantages, also introduces new challenges. While many interview participants acknowledged the potential behind pharmacogenomic drug development, many also noted the continuing limitations of these new technologies and cautioned against overbroad generalizations of the promise of personalized medicine. The rare disease context can introduce challenges in recruitment and may consequently result in smaller clinical trials that can reduce the robustness of clinical trial data, particularly the ability to detect safety concerns. Concurrently, the increasing use of biomarker-based enrichment strategies leaves open questions about where to establish diagnostic cut-off points and the potential lack of evidence on the use of the drug outside of the biomarker group. Ideally, if a pharmacogenomic test can reliably identify which patients are most likely to respond to a drug therapy, this may clarify which patients should have access to which drugs. However, where diagnostic test results are used to delimit treatment access, important questions emerge around the reliability of the test in identifying patients and the strength of the correlation between biomarker status and drug response. Further, the complexity of disease pathogenesis and the heterogeneity of biomarker expression can also make delineating access difficult. Although the appropriateness of clinical trial design will vary from case to case, the use of multi-arm trials or adaptive features in clinical trial design may help to improve the quality of the evidence for pharmacogenomic drug products.

Finally, as in all areas of drug approval, regulators and funders must balance the need for robust evidence of drug safety and efficacy with the need to provide timely access to promising new therapies. While there is a need for some flexibility in providing earlier access to drugs that treat rare diseases with few or no existing treatment options, there is also a need to maintain high standards of safety and efficacy before approving a niche market therapy. Given the evidentiary challenges in niche markets, increasing post-market surveillance and evidence generation after market entry will be an important step in counterbalancing any uncertainties that may exist at the time of initial approval (Gibson & Lemmens, 2014). Evolving evidence from additional post-market clinical trials and more independent studies based on real-world use are important to improving drug regulation generally and may be particularly important for ensuring the continued safe and effective use of niche market therapies (Gibson & Lemmens, 2014).
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Notes

Conflicts of interest: None declared.
Research for this paper was supported by a Genome Canada grant on Ethical and Legal Issues of Cancer Initiating Stem Cell Research.

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The authors would like to thank Dr. Saad Abughanm and Harleen Khanijoun for their earlier research on this project and their involvement in conducting interviews for the qualitative study. They would also like to acknowledge Nicholas Reist and Kelly Tai for their assistance with background research and references, and Brenda Robson for her help in editing this paper.

1. During interviews, a couple of participants observed that “personalized” medicine is not the most accurate term to describe targeted therapies since the treatment is not designed specifically for each individual patient (Regulator 5; Policy Expert 5). Similarly, some members of the scientific community now argue that “stratified” medicine is a more accurate term than “personalized” medicine for describing this new approach which targets patient subpopulations that are more or less likely to respond to a treatment rather than tailoring the treatment specifically for the individual (Trusheim, Berndt, & Douglas, 2007).

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