ETHICAL, LEGAL AND SOCIAL ISSUES IN DRUG DEVELOPMENT AND PHARMACOGENOMICs:
Report on a Qualitative Study of the Perspectives of Canadian Stakeholders

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Introduction

Study Methods and Objectives

Areas of Ethical, Legal and Social Concern
- Regulating in the Pharmacogenomics Context
- The Drive Towards Niche Markets
- Fairness of Study Design
- Cost Implications of Niche Markets
Introduction

Objectives

• Capture perspectives of key informants on different aspects of pharmacogenomic drug development, particularly the ethical, legal and social issues involved.

• Understand how different stakeholders view the opportunities and challenges of pharmacogenomics to provide insight into the regulatory and policy responses that are necessary to achieve the successful—and hopefully sustainable—integration of pharmacogenomic therapies into the health care system.

Methods

A total of 34 semi-structured interviews with key Canadian stakeholders, including:

• drug regulators,
• drug funders,
• health technology assessors,
• clinical researchers,
• patent experts,
• drug policy experts,
• pharmaceutical industry representatives (brand and generic) and
• patient advocates.
What is Pharmacogenomics?

Pharmacogenomics: the study of the influence of genetic factors on drug response. 

• Depending on each individual’s genetic makeup:
  • Some drugs may work more or less effectively.
  • Some drugs may produce more or few side effects.

Drug companies are developing an interest in increasing the efficacy of products by developing companion diagnostic tests.

• Ideally, the "one size fits all" model will give way to more “personalized” approaches where the "best-fit" drug can be identified at the outset.

“Until we have a much better picture – comprehensive perspective – on the genome instead of just these little snapshots, I really dislike the thought of overpromising to the public that genomics can really help them make meaningful decisions in their life, about their health. It’s disingenuous at best, it’s dangerous at worst.”

- Policy Expert
Regulating in the Pharmacogenomic Context

Coordinating the Review of Drug and Test Components

• For most pharmacogenomic therapies, the **companion diagnostic is an essential component in ensuring the safe and effective use of the drug product.**

• Health technology assessment procedures should take a **holistic approach** in assessing pharmacogenomic therapies and **consider both the diagnostic test and pharmaceutical product in tandem** to ensure the combination of the drug and companion diagnostic is effective.

Reviewing drugs and tests in tandem may help to establish their interdependence and increase the likelihood that both will be made available and funded together.

“[Drug funders] should be assessing the evidence behind the effectiveness and specificity and sensitivity of the test and how that relates to the treatment and then the effectiveness and cost-effectiveness of the treatment given the diagnostic test. At the moment that’s not clear that that’s being done.”

- Health technology assessor
The Drive Towards Niche Markets

Challenges of Modern Drug Development

• In recent years, the pharmaceutical industry’s research and development costs have been increasing steadily, while the number of new drug approvals has been declining.

• Many commentators predict the death of the blockbuster model of drug development.

• As more and more blockbuster drugs come off patent, industry is increasingly turning towards other areas of drug development, including pharmacogenomics, as a source of new drug discovery.

“The question is less about going after blockbuster drugs versus a niche product as it is [about] where are the markets—where is the medical need.”
– Pharmaceutical Industry Representative

“I would express a general concern that companies would see an advantage in developing drugs that require identification either of a receptor, or in particular a metabolic step, so that they could see an opportunity for them to create a niche and co-market a test,… give some exclusivity, … have a patent on the test as well as the product…”
– Policy expert
The Drive Towards Niche Markets

The Equity Problem

• There is a general concern in pharmaceutical development that drug companies, as for-profit ventures, are driven towards the most profitable markets—which often do not correspond with where the greatest medical need exists.

• Personalized medicine focuses on specific subpopulations, and therefore, it can increase the risk of health disparities.

• Pharmacogenomics is sometimes viewed as a trade-off between less expensive drugs that work in a broad population, and much more expensive drugs that are effective for only a fraction of the population.

“We felt it was in fact the responsible approach to actually figure out who is the best patient for the medicine... it’s actually unethical to not do it.”
- Pharmaceutical industry representative

“The question is: are we spending our energies and efforts on drugs that are going to be directed towards only a select group of individuals and what does that mean in terms of equity... and fairness.”
- Policy expert
As pharmacogenomic drugs are often narrowly targeted towards patients with a specific genetic marker, the population base on which to conduct clinical trials may be inherently limited.

Further, drugs for niche markets are sometimes fast-tracked during the drug approval process, particularly where they treat life-threatening conditions or where no alternative treatment is currently available. Researchers sometimes “enrich” study populations to identify a population of patients in whom a drug effect, if present, is more likely to be demonstrated.

For pharmacogenomic drugs, diagnostic testing may be used to enrich the study population by selecting only biomarker-positive patients who are more likely to respond to the drug—a strategy known as “predictive enrichment”.
Finding the Right Balance in Enrichment Design

While predictive enrichment may lead to smaller, more efficient clinical trials through targeted patient selection, significant problems may arise if such studies are not properly designed—particularly where the scientific basis for selecting patients is unsound.

- Biomarker groups who are unlikely to respond to a drug should likely be excluded if there are alternative treatments available. More importantly, if a genetic test can accurately predict severe or likely adverse drug reactions, fair subject selection may require excluding certain biomarker groups.
- On the other hand, where the correlation between the biomarker and the targeted therapy is weaker, excluding certain biomarker groups may be problematic.

“Patients should have all the power to assess their risk... Patients are the ones who are taking all the risk—we’re the ones taking the drug into our body.”

– Patient Advocate

“A lack of evidence does not necessarily mean a lack of benefit... and were dealing here in a world where there isn’t a whole lot of evidence.”

– Patient Advocate
# Fairness of Study Design

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<th>Potential Responses</th>
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| **Multi-arm clinical trial**: trial conducted in biomarker-positive, biomarker-negative and control groups. | • Ensures that drug is tested outside of the biomarker group.  
 • Helps to refine the line between responders and non-responders. | • Trials may be more complex and time-consuming.  
 • Potential ethical problem of exposing biomarker-negative patients to drug they are unlikely to respond to. |
| **Follow-up studies** that test the drug outside of the initial biomarker group. | • Allows the drug to be approved faster for the initial biomarker group through targeted clinical trials.  
 • Only patients who are most likely to respond are subjected to the drug. | • May be significant delay in conducting the follow-up studies.  
 • Uncertainty over who should fund/conduct the follow-up study, or how regulators would enforce such a commitment. |
Cost Implications of Niche Markets

Dynamics of Niche Markets

• Where a disease is rare—and particularly where its life-threatening—and there are few, if any, alternative treatments available, it becomes politically untenable for drug funders to refuse to cover what may be the only treatment option available to those with the condition, even if the drug is extremely expensive.

• Moreover, there is little competition in niche markets, which means that there are usually no competing products to help drive down prices and the ability of drug funders to negotiate for lower drug prices is thus compromised.

“I don’t want to be cynical, but the fact is that none of the targeted therapies are cures... So companies make their money over the long term versus short term. So the drug company has got a patient for life.”
- Scientist

“The niche-busters seem to be working on the basis that while it’s a small patient population, and industry is saying we can’t defray our costs across a large population and therefore keep the prices down. They’re really using the political economy of rarity, if you like, to justify very significant payment.”
- Health technology assessor
Cost Implications of Niche Markets

The Issue of Cost

• As the number of niche therapies entering the market continues to increase, there is growing concern over how long healthcare systems can sustain this pricing model.
  • Some new pharmacogenomic drugs may cost tens or even hundreds of thousands of dollars for a course of treatment.
  • While many stakeholders understand the basic rationale for high prices in niche markets, there is also significant suspicion that industry may be gaming the system in order to justify very high prices.

“If the industry is saying that the pricing is dependent upon the number of beneficiaries of the drug, or people you might use it, and they start expanding the number of beneficiaries, presumably there would be some price reduction—that follows from the logic that the industry itself uses.”
  – Policy Expert (economist)

“The signal that you send first by what you pay and how much you pay for it actually plays a whole feedback loop to the industry as a signal to what we can develop and where the money is.”
  - Regulator
Cost Implications of Niche Markets

Improving Coverage Decisions

Further, uncertainty around the duration of treatment and the size of markets will likely make funders reluctant to cover these often highly expensive drugs without some mechanism to control the potential cost implications.

- **Coverage with Evidence Development (CED):** Healthcare decision-makers in various jurisdictions are showing growing interest in CED, one of several terms used to describe “conditional” reimbursement models where funding for therapeutic interventions is provided on a time-limited or conditional basis to allow for the collection of real-world data around its safety, efficacy and cost-effectiveness.

"As patient advocates, we’re all in favour of programs with evidence development and were in favour of getting the innovative drugs to market faster.”

– Patient Advocate
“There is always a concern about who’s not getting treatment and who’s going to be excluded. It’s a real concern that only those patients with a specific genetic mutation will have access to any therapy. So it’s a bit of a crap shoot if you end up with the right type of cancer—whether it’s one that’s currently under research for a genetic mutation or not.”

– Patient Advocate