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KEY DISCUSSION POINTS & RESEARCH PRIORITIES RAISED AT CIHR SEX, DRUGS, AND GENES WORKSHOP

Held in Montreal on October 2nd, 2015

Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Contents

Executive Summary of Key Points and Research Priorities

Personalized medicine is a strong contender to begin to break through the stagnation in drug therapy, through improvement of clinical biomarkers and pharmacogenomics, as well as interactions between sex-related variables and genetic variables.

Research priority #1: Assess the merits of using pharmacogenomic (PGx) data in the real world, primary care setting

- Evidence is needed showing that the use of PGx data improves patient outcomes and reduces adverse effects
- Literacy of the public and of health care professionnals needs to be improved

Research priority #2: Integrate sex as a variable in pharmacogenomic research and personalized medicine

- More research is needed on the effect of sex and sex hormones on PGx, both in basic science and clinical research
- The effect of sex and sex hormones on pharmacokinetics, pharmacodynamics remains poorly understood
- Sex-drug-gene interactions are currently under-studied
- Clinical trial data should be disaggregated by sex to better inform both research and practice
- Research needs to consider that age may interact with sex, as a function of sex hormone levels and genetic regulation at different stages of the life cycle
    - For example, an explanation is needed as to how variations in sex hormones modify drug efficacy, safety and toxicity in male and female adolescent youth
- Sex-drug-gene interactions need to be studied in the context of polypharmacy in order to be generalizable to men and women with multiple chronic conditions

Research priority #3: Acknowledge the complexity of personalized medicine

- Research is needed that embraces this complexity and avoids the reductionist approach inherent in studying the one disease–one drug model

Research priority #4: Proof of principle vs. proof of value

- Pragmatic clinical research is needed that combines treatment efficacy with cost-effectiveness in order to incentivize health care settings/systems to transform care and implement personalized medicine

Research priority #5: Methodological innovation in the area of reverse-translational medicine

- Fund research that starts with the observation of sex/gender differences in pharmacoepidemiology/administrative datasets and/or large drug trials, and use these data to inform pharmacogenomics research into drug safety and efficacy

Research priority #6: Support implementation science to scale up the use of personalized medicine clinics in Canada

- Fund research that determines whether the development and use of diverse new software and genetic tests help with clinical decision-making

Research priority #7: Engage stakeholders to analyze the increase in overall efficiency in healthcare delivery when personalized medicine is implemented

- For example, consider the savings if a single panel of tests were to inform the prescription of 6 different drugs, at the right doses, to the right person

Intriguing research questions

- In the context of SPOR and Innovative Clinical Trial Designs, is there merit in exploring how to recruit greater numbers of women to clinical trials?
- If sex hormones are important gene regulators across the life span, should we find a more reliable way to measure sex hormones in clinical practice?
- Should these questions be considered by CIHR's Ethics Advisory Committee on Innovative Clinical Trials?

The critical question: Does Canada have the capacity to be a leader in this space?

The answer is yes. The ethical issues around genetic testing are being addressed. There is a strong PGx research base. IGH has taken the lead in building capacity around the measurement of sex and gender-related drug-gene interactions. DSEN oversees centres with access to large administrative databases. The provinces and CIHI have integrated population datasets that can be mined. Finally, personalized medicine clinics already exist in Canada that can be scaled up and studied with respect to improving patient outcomes.

Introduction

The *Sex, Drugs, and Genes* workshop, held in Montreal on October 2nd, 2015, brought together experts from across Canada to discuss sex, gender, pharmacogenomics, personalized medicine and related issues.

This report details the points raised by participants during workshop discussions. It groups topics thematically, even where discussion occurred at several distinct points over the course of the day.

Workshop Programme

2 October 2015

8:30 – 8:45	Welcome and opening remarks *Paul Lasko on behalf of Jane Aubin, Chief Scientific Officer, Vice-President of Research CIHR*
8:45 – 9:00	Overview and Purpose of the Workshop *Cara Tannenbaum, Scientific director, CIHR Institute of Gender and Health*
9:00 – 10:45	Roundtable and Discussion 1: Existing Knowledge of Sex-Drug-Gene Interactions at the Molecular and Cellular Level *Chantal Guillemette, Professor, Université Laval* *Jean-Claude Tardif, Montreal Heart Institute* *Marie-Pierre Dubé, Montreal Heart Institute* *Discussion facilitated by Steve Robbins, Scientific Director, Institute of Cancer Research*
10:45 – 12:15	Roundtable and Discussion 2: Clinical Practice Interventions to Prevent Sex-Drug-Gene Interactions *Martin Dawes, Royal Canadian Legion Professor and Head, Family Practice, UBC* *Richard Kim, Professor of Medicine, University of Western Ontario* *Rod Rassekh, Pediatrics (Division of Peds Heme/Onc/BMT), UBC* *Discussion facilitated by by Paul Lasko, Scientific Director, Institute of Genetics*
13:00 – 14:30	Roundtable and Discussion 3: Health System Change – Looking Towards the Future *Bruce Carelton, Director, Pharmaceutical Outcomes Programme, Pediatrics, UBC* *Katherine Bonter, Director of IP at MHI; of Commercialisation at PCITP.* *Robert Peterson, Director, Drug Safety and Effectiveness Network, CIHR* *Moderated by Cara Tannenbaum, Scientific Director, Institute of Gender & Health*
14:30 – 16:30	Open Discussion on Future Research Priorities

Part I Drugs and Genes: Pharmacogenomics and its Stumbling Blocks

1 The Existing Context

- Clinical practice and drug therapy are currently at an impasse as they face the new challenges and opportunities presented by personalized/precision medicine approaches
- Medicine is traditionally seen by practitioners as a binary system: treatment either works or doesn't work, and is designed for the perfectly average person within one standard deviation
- The truth is that 20–60% of patients do not respond effectively to the drugs administered by clinicians, for example for hypertension, diabetes, and primary and secondary prevention
- It is urgent to understand why the same drugs have such different results in different people
- Even where we are certain that a drug is effective for an average patient, many patients are not average: everyone is an outlier in one context or another
- Complexity arises for patients who have multiple chronic conditions and who need to take 5 or more medications (polypharmacy)
- Some patients are taking e.g. twenty different drugs: de-prescribing may be the answer to improve their health
- Primary care practitioners are increasingly frustrated by this prescription environment
- In the cardiovascular field, few new drugs are coming to market
- The vast majority of large clinical trials *fail*
    - A large percentage even do so at phase 3, while at the same time an increasing proportion of treatments are approved based on phase 1 and phase 2 clinical trials
- One reason is that it has become difficult to outperform existing treatments while in the past the competitor was a placebo
- Oncology and rare diseases may be facing fewer difficulties
- In oncology, genetic markers are easier to obtain as tumour biopsies are more accessible while for rare diseases the clinical phenotypes are more profound
- In the 1960s the survival rate was 30% for a given cancer; now it's 90%
    - To get the last 10% we don't need new drugs
    - We only need to better understanding the existing drugs
    - We need to decide where to turn to improve this understanding

Personalized medicine is a strong contender to begin to break through this stagnation, through improvement of clinical biomarkers and pharmacogenomics, as well as interactions between sex-related variables and genetic variables

2 Genomic Data

- Pharmacogenomics is only useful if testing is available at the right clinic, at the right time
- Researchers are focusing on genotyping the same genes they were looking at in 2006
- Existing knowledge is concentrated within certain genes
- Large-cohort data may change this, but remains expensive and non-trivial to analyse
- DNA sequencing in clinical trials should become a mandatory rather than a voluntary option
    - Currently only ¼ of participants opt-in, meaning the trial might have to be repeated to get statistically significant results on genetic parameters
    - Barriers include fears that mandatory sequencing will undermine participation levels
- It remains the case that huge reports like those provided by 23andMe are of very little use
- Need linkages between EMR and Genotyping data
- Most clinicians do not use pharmacogenomics in the clinic because they are still not convinced it leads to improved outcomes and/or do not have the required genetic knowledge

Research priority #1: Assess the merits of using pharmacogenomic (PGx) data in the real world, primary care setting

- Evidence is needed showing that the use of PGx data improves patient outcomes and reduces adverse effects
- Literacy of the public and of health care professionnals needs to be improved

3 Biomarkers

- Why not include more “old-school” forms of personalized medicine alongside pharmocogenomics?
- Looking at more easily ascertainable patient characteristics, e.g. sex, age
- These must be understood in their full, intra-patient context, e.g. diet, disease
- It is beginning, but very few people practice it
- It is also important that Canada figure out what information is clinically useful
- As well as what other technologies can be brought to bear
- Drug alert software, genetic testing, practice guidelines, drug approval, surveillance post-marketing, may each be relevant

4 Sex chromosomes

- The X chromosome has 1,669 genes and the Y chromosome has 426 genes
- Several cancers and immune responses are associated with the X chromosome in genome-wide association studies (GWAS)
- However only 33% of GWAS studies consider the sex chromosomes, so we may be missing important associations
- A growing body of literature suggests that sex hormone regulation of the autosomes may explain known sex differences in the epidemiology of disease and response to treatment
- This is a relatively new field of investigation

Research priority #2: Integrate sex as a variable in pharmacogenomic research and personalized medicine

- More research is needed on the effect of sex and sex hormones on PGx, both in basic science and clinical research
- The effect of sex and sex hormones on pharmacokinetics, pharmacodynamics remains poorly understood
- Sex-drug-gene interactions are currently under-studied
- Clinical trial data should be disaggregated by sex to better inform both research and practice
- Research needs to consider that age may interact with sex, as a function of sex hormone levels and genetic regulation at different stages of the life cycle
    - How do variations in sex hormones modify drug efficacy, safety and toxicity in male and female adolescent youth?
- Sex-drug-gene interactions need to be studied in the context of polypharmacy in order to be generalizable to men and women with multiple chronic conditions

Part II Accounting for Sex and Gender in Personalized Medicine

5 Participation Levels

- Accounting for sex and gender in personalized medicine seems intuitive, but is rarely done
- Only one third of research participants are women, and this percentage is even lower in Phase 1 and Phase 2 studies, so we are underpowered to draw conclusions about the efficacy, safety and tolerability of treatment in many cases
    - Only 28% of clinical trials disaggregate results by sex
    - Acknowledgement that this makes it difficult to deliver personalized treatment to women
    - Some participants claim that in non-oncology research, the real numbers are even lower
    - Multivariable analyses control for sex, but do not stratify (or disaggregate) results by sex, rendering it impossible to tailor treatments to men and women separately
- This, despite precedents by the FDA to approve drugs for men or women only, based on sex-specific efficacy
- There have also been cases where the recommended dose of a drug differs for men and women, independent of body size and weight
- We do not have a simple answer why fewer women are included in drug trials
    - One participant suggested research participants are a distinct population who move from study to study, and claimed that this is a “male” way of acting
    - The participant also suggested the possibility of a “risk-taking” element
    - Are male college students motivated to enroll in Phase I and II drug trials to get free food? If so, this becomes a gender issue
    - It would also be worthwhile to understand what is unique about the women who *do* participate in these early phase studies
    - Some felt that women are discouraged from participating in trials through their families, so the whole family should be involved, not just the patient; others felt this view was paternalistic
- It may also be that investigators running clinical trials simply are not prospectively asking themselves what kind of environment and steps are necessary to attract and retain female participants
- Participation depends on society
    - It is not just women who are responsible for low participation, but society and research projects are structured in ways that make it difficult for them to participate
    - Their life experiences and barriers are not taken into account
    - Special counseling may be needed for women in clinical studies
    - Broader strategies must be developed to increase recruitment of women
- Do we need to require follow-up studies to make sure we reach the numbers we need?
- If not, we will have limited power to perform interactions by sex: individually within trials and GWAS, giving rise to two questions:

    - Should it become mandatory to accrue sufficient sample size to stratify by sex?
    - When we test whether there is statistical interaction, it is multiplicatively larger. Is disaggregation sufficient or should we also be looking for complex sex interactions?
- X and Y chromosomes should no longer be ignored in GWAS studies. Past studies should be revisited to perform such analyses, with small-scale funding incentives.
- Why are we not studying and tracking whether the placebo response varies between men and women?
- Perhaps if Canada really wants to be unique, the time is right for women-only studies to see how women will respond
    - One participant submitted a protocol for a women-only hypertension study and asked for CIHR funding
    - They told her she should include men
    - Another participant noted that as much as she would love women-only trials, men need to be included if for no other reason than to tease out the effects: she thinks we're going to find some really interesting results
- We need to ascertain the right way to approach sex-gene interactions in clinical trials in general
- The same problems recur in fundamental research done on animal populations
    - Male animals have tended to be studied
    - One US primate researcher claimed that females were "too complicated"
    - Some may also believe accounting for female subjects makes research more expensive
    - Problematic for the pro-animal approach is that enzymes are not necessarily regulated the same way, and research does not necessarily translate to human genes at all
    - Most models for studying sex differences differ between animals and humans, and may not be transferable between the two
    - We should try to reach consensus about the appropriate model
- The problem is not unique to animals, but also cell status: We do not always know a cell's sex, which is important

Intriguing research questions:

1. In the context of SPOR and Innovative Clinical Trial Designs, is there merit in exploring how to recruit greater numbers of women to clinical trials?
2. If sex hormones are important gene regulators across the life span, should we find a more reliable way to measure sex hormones in clinical practice?
3. Should this be considered by CIHR's Ethics Advisory Committee on Innovative Clinical Trials?

6 Relevant Variables and Biomarkers

- A separate issue from research participation rates are gender- and sex-associated biomarkers and other variables that are (or are not) recorded and analysed
- Researchers need to start looking for sex- and gender-based differences
- This is a critical time to have these variables included within personalized medicine: the field is ready for implementation
- On the question of what sex and gender differences we can and should capture, most thought that observational sex differences should not be dismissed
- Critical sex examples are:
    - Germline biomarkers, which is information that we do have. It would be easy to merge both together in oncology
    - Sex hormones, which can and should be measured in drug trials
- Estrogens were discussed quite a lot: there is still a lot to be learned about how estrogen regulates gene expression.
- There appear to be sex differences in the metabolizing enzymes, such as the cytochromes, but both these and other pharmacogenomics variables like SNPs, need to be further investigated
- Clinicians should collect broad patient data, including genotype and phenotype, instead of relying on self-selecting research participants, so that current practice can inform future practice
- Subcategories are also extremely important, such as pregnant women, post-menopausal women, etc.
    - One participant described research that found similar reactions in men and pre-menopausal women, but completely different results for post-menopausal women
    - All these variables need to be tracked
- Metabolism is clearly important also, especially with respect to drugs, and is related to stressors, which may have a relationship to gender
- At least some aspects of lifestyle should be incorporated
- We may want to track results of men who have more estrogen, e.g. due to obesity, or the results of transgender men who take estrogens
- Analysis should consider both sex and gender
    - Gender has a huge role in what's prescribed, what's taken, especially in mental health and pain
    - Related variables like race, age, kids, and combinations of these
    - Obesity is another variable we tend to ignore
    - Transgender and transsexual people might have different incidences of heart disease, etc., in certain situations
    - All are important to monitor in post-marketing surveillance, pharmacovigiliance

7 Secondary Analysis and Meta-analysis

- Existing data sets can be reanalyzed or combined: there is huge potential for discovery
- Even if a previous study did not look at sex data, we should re-run the analysis based on sex
    - One participant, however, raised the restrictiveness of consent forms
    - The purpose of the initial research might restrict this kind of re-use
- Nevertheless, the practice is popular and getting a lot off attention and press
- In Canada, we have many administrative databases; the single-payer system means that the governments of each province collect healthcare and innovation data
    - These data might identify signals where there would be a difference between men and women. These findings could be use to inform future pharmacogenomics research
    - Potentially integrate these data sets cross-province
    - If GWAS studies already lack the power to study sex-drug interactions, and we now want to add an additional set of variables (those linked to gender and sex), we may want to lead linkage of data sets internationally
    - Another idea is to link data from trials across a family of drugs to increase the sample size
    - There are various strategies that can increase the power to find associations
    - The principles will be cost-effectiveness, scalability, doing no harm
    - Think about how to use existing information to identify important differences in response or effectiveness between sexes
- The aim is to identify markers that increase pre-test probability that an individual will respond to a drug

8 Overcoming the Obstacles

- One strategy is to debunk exaggerated claims that “pure” genomics is the key to personalized medicine
- Genomic research entities looking for funding are forced to make huge claims about what their research will achieve
- Patients are coming and demanding tests, magic bullets
- They assume that we have already done all of this:
    - That we know the different effects on women, men, etc.
    - They are not familiar with the idea of making study samples as homogeneous as possible
- So when things go wrong, they will blame physicians, pharmacists, and hospitals: not the process
- Therefore, we need to get on this very quickly to live up to expectations
- Realistic appraisals of genomics research are also important in terms of keeping the issue of potential harms in our mind
- Genomics approach basically means drug treatment: we need to be concerned about toxic effects

- Look at the broader picture that may open the door to other forms of intervention e.g. reducing polypharmacy in the elderly
    - The answer is not more analysis of drugs, but reducing the number and amount of drugs being taken concomitantly
- Patient demands can be stressful, but they should also inform research
    - Avoiding adverse drug reactions ranks highest on the list of patient priorities for healthy aging

Research priority #3: Acknowledge the complexity of personalized medicine

- Research is needed that embraces this complexity and avoids the reductionist approach inherent in studying the one disease–one drug model

Part III Catalysts to Change Clinical and Research Practice

9 Necessary Evidentiary Basis for Enhancing Effectiveness and Safety

- There was no consensus in this topic, but much interest
- Some felt future advances should only be implemented on the basis of hard data, preferably very large clinical trials
    - A change in practice based on substandard data could negatively affect billions of people, so these changes should really be based on large studies, including many millions of participants
    - Observational evidence may not be enough, but should be used to inform new methods of analysis
- FDA and Health Canada give examples of the Cardiac Arrhythmia Suppression Trial (CAST) study
    - Premature irregular beats in heart attacks
    - If you eliminate premature beats the hypothesis was that people will live longer
    - In fact in the CAST study the drug removed the beats but people died sooner
- When challenged, there was some acknowledgement that change can legitimately made by informed, expert practitioners based on much smaller datasets that can nonetheless yield compelling results, rather than waiting seven years for a new trial with robust evidence
    - But this, it was still argued, does not justify widespread changes to practice
- Another argument from the opposing view was based on the fact that clinicians are not currently practicing with an evidence-basis approach
    - They are prescribing off-label use more than on-label use
    - They are not using existing trial data
    - So what makes anyone think that with more trials, physicians will suddenly begin to do so?
    - This research is diverting huge amounts of money for no real reason
- Are demonstration projects necessary, in real care?
    - Policy makers require demonstration projects that show cost-effectiveness
- The conclusion was that physicians need more than biomarker information
    - Practice will change, but only in response to research work that demonstrably translates into actionable recommendations that will change outcomes
    - Do we know prospectively that these huge studies will tend to change outcomes in a cost-effective way?

Research priority #4: Proof of principle vs. proof of value

- Pragmatic clinical research is needed that combines treatment efficacy with cost-effectiveness in order to incentivize health care settings/systems to transform care and implement personalized medicine

10 Bedside to Bench: Reverse-Translational Approaches

- In the context of money allocated to a strategic initiative, if the goal is to better understand the effect of sex differences, usually we move from the basic science up to the translational piece, the population
    - But perhaps we should be innovative and look at it from the reverse direction: many drugs that are used could be looked at in terms of safety, looking for sex-based differences
    - From there go back down to the biological level and try to explain why these differences exist
    - It's still a kind of translational approach, but it's reverse-translational, to better understand and care for patients
    - We have many drugs already, why not better understand the ones we have?
- For example, it was observed that Asian female non-smokers had very different disease profiles that dramatically increased the probability of certain mutations
    - This led to the identification of certain mutations and arrangements, and a dramatic transformation in the way these patients are treated
    - This pushed the field forward, and demonstrates that you have to sometimes go back to the observational field, which helps inform research questions
- Starting from the population level and real-world data and outcomes could ensure that policy decisions and real-world drug use is based on real-world study, which might actually be better, although currently it is seen as inferior
- Real-world settings are important
    - One limitation of randomized trials is enrolment criteria: we need more data on the extremes
    - E.g. aging populations, drug metabolism and dosage changes that were not predicted
- Observational studies offer information that may be missing in RCTs
    - Design and methodology could include measurement of broader factors e.g. gender, roles, structures, societal factors that may influence gene expression
    - Fairly simple to genotype participants in cohorts

Research priority #5: Methodological innovation in the area of reverse-translational medicine

- Fund research that starts with the observation of sex/gender differences in pharmacoepidemiology/administrative datasets and/or large drug trials, and use these data to backwards inform pharmacogenomics research on drug safety and efficacy

11 New Tools and Practices

- One need is to build powerful, predictive tools allowing us to plug in a patient's sex, gene, gender characteristics, use of other medications, and generate the probabilities of drug response and of harm
- E.g., detection of a genetic mutation that increases the risk of thrombosis with the use of the oral contraceptive pill
    - What is the best approach?
    - Routine genetic testing for all reproductive age women seeking methods of contraception?
    - If so, how?
- One standard, two-step approach to transform the way we practice medicine:
    - build a fear
    - create a solution
- Case in point. Look at the attention that antibiotic resistance is getting. If we can test for e.g. specific microbes based on DNA, or host response based on genetic variation, we may be able to reduce microbial resistance. Start with microbial resistance and antibiotics, and then scale up to chronic disease.
- Beyond orally ingested drugs, consider also those administered with some other device, e.g. injection. The administrative device might be important: should we use the same device for men and women? Absorption of the active ingredient in generic formulated drugs is different for men and women based on the filler.
- Pre-emptive genotyping may be practicted in the future, before people walk through the clinic doors.
    - Does research have a place in making that happen? How will these goals be achieved? Incentives? Levers? Catalysts?
- BC has online systems that can integrate a pharmacogenomics aspect. Electronic medical records will need to have access to this data, which will be kept in provincial databases. Educational software will then be needed to link the patient's phenotype to treatment according to clinical guidelines. Physicians will not be able to remember all the combinations and permutations. A system is needed to integrate all these elements into systematic practice change. It is feasible if we work at it incrementally. Start by targeting the information needed in a certain context. A number of personalized medicine clinics already exist in Canada that do this successfully.
- A rare genetic polymorphism that leads to ADR is more common in Thailand, but a large proportion of the Thai population has been genotyped for this one particular ADR, and it is in people's medical record. So this is doable.

Research priority #6: Support implementation science to scale up the use of personalized medicine clinics in Canada

- Fund research that determines whether the development and use of different software and genetic tests help with clinical decision-making

12 Ethics, Legality, Privacy, and Other Regulations

- These issues are already being addressed to a large extent by the projects funded under the 2012 Large Scale Applied Projects co-lead by Genome Canada and CIHR
- Regulatory agencies can foster data transparency and data sharing
- Before doing pre-emptive genetic banking, the legal and ethical policies and laws and privacy interests, discrimination and insurance have to be addressed to get patient buy-in
- We need to know that as patients, our data will be safe
- We need genetic data in the health record, because we need to link it to treatment decisions and other info for the data to be meaningful
    - Incorporating genetic information into medical records is already happening, e.g. in Estonia where there is 95% coverage using the same universal ID # card that Estonians use to pay parking fees
- New strategies are being rolled out, e.g. the Personalized Medicine Initiative (US) is creating a cohort of 1 million
    - They are putting decision-making and ownership in the hands of patients
    - They decide what is going to happen with the data, which overcomes a lot of issues and barriers
- Pre-emptive genotyping comes with the ethical question of the "right not to know"
    - When you have e.g. info about increased risk of a condition for which no treatment exists, how do we decide what information patients need/want?
- Implied consent may be important: UK has an opt-out clause for GWAS studies

Critical question: Does Canada have the capacity to be a leader in this space?

- The answer is yes: The ethical issues around genetic testing are being addressed. There is a strong PGx research base. IGH has taken the lead in building capacity around the measurement of sex and gender-related drug-gene interactions. DSEN oversees centers with access to large administrative databases. The provinces and CIHI have integrated population datasets that can be mined. Personalized medicine clinics already exist in Canada that can be scaled up and studied with respect to improving patient outcomes.

13 Pharmacoeconomics and Practical Barriers

- How can we get answers about sex-drug-gene interactions to patients at the right time, place, and cost?
    - This includes logistics and feasibility within a local context
    - Not just scientific barriers, but hospital and funding barriers
    - How to start a franchise that becomes valued, then scale it up to yield transformative impacts?
- Health economics has perhaps not been discussed enough
    - We discussed initiatives to insert personalized genomics into practice
    - We did discuss proof of value, which tends to be driving care as much as proof of principle
    - A bit of a catch-22: if you prematurely start looking at economics, the value depends on the strength of the clinical economics
    - Even if the economics make sense, it does not inform implementation at the clinical level
    - A small minority of people in the room include economics in their studies, but not all of them have faith in it
    - It may not provide meaningful numbers as far as clinical practice
    - Papers have been written on this, but they tend to be theoretical
    - We are now ready for real-world economics
- From an HTA perspective, which inserts context, having any economic data from Canada, even if it may not be the greatest, would be extremely useful as a lever to drive improved care
    - Currently our economic data come from elsewhere or are being modeled
    - From a drug-relation approval and assessment of value perspective, we need to find ways of talking about money that are real, Canadian, and can scale up to practice
- One participant expressed that CIHR should take the lead on this alone (i.e. without industry)
- Does Canada have capacity to tackle the health economics aspect of transforming care? Or should we just look to the UK, who seem to do it well
    - On the one hand, showing cost-effectiveness in the Canadian context seems necessary
    - Hospitals in Ontario have every penny accounted for, though this is not true of all provinces
    - Each patient can be identified and followed in terms of cost
    - We need additional incentives to have hospitals and provincial administrative database work with CIHR to see if they can pull out real-world data costs
    - How can we better engage our stakeholders to address the practical economic questions?
    - CIHR-type funding initiatives might engage hospitals to pull out and publish their data
    - A modeled economic analysis might not appear credible, whereas real hospital data might get more traction to lead efforts to transform patient care

Research priority #7: Engage stakeholders to analyze the cost redirected elsewhere by implementing personalized medicine, leading to increasing system effectiveness

Imagine the resource savings if a single panel of tests informed the prescription of 6 different drugs, at the right dose, to the right person?

Part IV Participant-Identified Research Priorities

14 Role of sex hormones and age in adverse drug events

- Preclinical, observational, and clinical research investigating sex-drug-gene interactions with both men and women as participants
- Sex and gender-based analysis (SGBA) in drug safety & effectiveness along the lifecycle
- SGBA (including age and ethnic variation) in pharmacokinetics & pharmacodynamics to optimize drug efficacy
- SGBA in drug dosing
- Hormonal influences on pharmacogenomics (PGx) *in vivo* and *in vitro*
- Can PGx reduce adverse drug reactions?
- Age was identified as an important factor that warrants further study

15 Knowledge Translation & Implementation Science

- How to improve our current practice in bringing personalized medicine and pharmacogenomics from bench to bedside
- Patient and knowledge user engagement in pharmacogenomics (PGx) and pharmacoepigenomics
- Investigating effective implementation of personalized medicine in a real world setting
- Ways to encourage women to enroll in early phases of clinical trials
- Investigate how gender of physician and/or patient affects the likelihood of the type of drug the patient is prescribed (why there is gender-bias despite evidence)

16 Methodology & Open Access of Big Data

- Development, or use of, uncommon or new evaluation methods for testing drug efficacy beyond randomized clinical trials (RCT); evaluation of adverse drug reactions must be done in a real world setting
- Development of predictive models based on demographic characteristics (sex, age, ethnicity) on 2- or 3-way interactions (sex-drug, sex-drug-genes, etc)
- Prospective studies should leverage administrative/secondary data to explore sex differences in PGx on a population level (with public health implications)
- Provide incentive to researchers and physicians to allow their genotype data to become available and form research networks for study in this area (i.e. harmonize datasets)

Participant List

Flamine Alary, CIHR IA
Gillian Bartlett-Esquilant, KT researcher
Katherine Bonter, KT Intellectual property expert
Bruce Carleton, pediatric oncology pharmacist
Abby Collier, pharmacokinetics researcher
Janet Currie, patient advocate
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