



Biomarkers for Precision Medicine Initiative

National Workshop Report

November 19-20, 2009

Toronto Airport, Sheraton Gateway Hotel

An initiative led by the Canadian Institutes of Health Research (CIHR), Institute of Circulatory and Respiratory Health (ICRH), in partnership with:

Institute of Cancer Research (ICR)
Institute of Gender and Health (IGH)
Institute of Health Services and Policy Research (IHSPR)
Institute of Infection and Immunity (III)
Institute of Musculoskeletal Health and Arthritis (IMHA)
Institute of Neurosciences, Mental Health and Addiction (INMHA)
Institute of Nutrition, Metabolism, and Diabetes
CIHR Canadian Longitudinal Study on Aging Initiative (CLSA) & Institute of Aging (IA)
CIHR- Regenerative Medicine and Nanomedicine Initiative (RMNI)

Background:

Biomarkers are biological indicators that can be objectively measured to reflect an individual's biological status. Biomarkers, when validated, can serve as important tools for management of acute and chronic diseases. Specifically for an individual patient, biomarkers can help to define baseline risk factors in disease progression, clinical diagnoses, managing therapies, and predicting outcomes. Appropriate biomarker panels can assist in new drug, device and care model delivery development. Predicting complications of illness and allowing risk stratification help to achieve personalized approaches to treatment, and preventions in arenas such as cancer, diabetes, musculoskeletal health, neurosciences, cardiopulmonary, infectious and inflammatory, and aging processes amongst others.

It was the workshop organizers' hope that the national biomarker workshop would bring together many diverse and expert people from CIHR Institutes, partners, public research institutions, private sector therapeutic and diagnostic companies, not-for-profit, policy domains and others to work collaboratively and shape a unique and powerful direction for Canada with regards to biomarkers and human health. It was also hoped that the initiative would contribute to CIHR's mission by creating programs that advance world-class excellence in biomarker discovery, validation and application, to fulfill the mandate of early risk and disease identification, as well as chronic disease



management. These are part of CIHR’s overall strategic plan, on patient oriented research, personalized medicine and chronic disease innovations.

At present, there are many promising marker candidates available including those derived from biological experiments, genomics, proteomics, metabolomics, DNA sequence analysis, epigenetic changes, imaging, and phenotypic analysis, existing in many diverse databases in Canada and internationally. Hence, it is time to link platforms of discovery with networks of validation, with well-phenotyped and followed cohorts and trial data, in order for the evolving predictive and precision medicine to reach reality.

This biomarker workshop brought together basic and clinical researchers, health services and population health researchers, and other key stakeholders together to synthesize the state of art, and to identify compelling research priorities, defining gaps in the arena of biomarker discovery, development and implementation wherein a Canadian initiative could make a distinctive impact.

The purpose of this report is to share the discussions, ideas, and recommendations from workshop participants with other stakeholders. It is our hope that the feedback we receive from the community on this workshop report will help the CIHR Institute of Circulatory and Respiratory Health and partners to develop a Request for Applications (RFA) on the topic of biomarkers for better human health.

Brief description of workshop program (Day 1):

Plenary Session I: The Personalized Healthcare Imperative – Where Biomarkers Fit. (What are biomarkers, that is, how are they currently defined? Why are they important in the public and private sectors? Where are the great opportunities to make a difference through biomarker solutions?)

Speakers: Tim Triche, Jean-Claude Tardif, Mohammed Karmali, Pavel Hamet

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Plenary Session II: Quality Measurement of Biomarkers. (How do we assess and measure biomarkers? What are key considerations in this regard?)

Speakers: Cynthia Balion, Shana Kelley, Christoph Borchers

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Plenary Session III: Taking Biomarkers from Discovery to the Clinic (How do we extract value from complex data sets? How should multi-disciplinary teams work? Which cohorts for which question? Which molecular signature should we measure? How do we manage biospecimens? How do we achieve rigour in analysis without paralysis? How do we followup on biological leads? What is pharma’s perspective on biomarkers? What are the social and economic considerations in developing biomarkers? How do new biomarker tests/panels reach the healthcare systems?)

Computational Excellence - Rob Balshaw

Seamless Teams - Janet Wilson-McManus

Cohort Identification & Management - Don Sin, Jolanda Cibere

High Performance Platforms - John Wilkins, John Rioux



Harnessing Engineering & Nanosciences - David Juncker
Biospecimen Management - Peter Watson
Validation & Qualification - Agnes Klein
Extracting Biological Value - James Woodgett
Perspective of Investigators - Jennifer Van Eyk
Perspective of Imagers - Robert Bartha
Pharma's Needs - David Brener
Diagnostic Industry's Perspective - Sean Higgins, James Donnelly
Social & Economic Considerations - Carlo Marra
Bioethical Consideration - Ron Heslegrave
Bridging into the Healthcare Systems - François Rousseau

Addressing Questions from Day 1

Brief Overview:

Day two opened with a brief review of the first day and an outline of the second day agenda, followed by general discussion on the key messages from Day one. The morning program continued with a presentation on biomarkers discovery and development from the National Institutes of Health (NIH) perspective, followed by nine breakout sessions during which participants discussed key biomarker issues, data gaps and research opportunities. The day continued with brief reports from the breakout groups, final discussion among participants on the key elements for a Request for Application (RFA), and ended with short summary outlining next steps for RFA formulation and launch.

Participants' key comments on presentations and discussion from Day 1:

- Many participants mentioned that **young investigators** in the biomarker discovery/development field require support and nurturing. There is need for research focused on large scale multidisciplinary biomarker projects and for **trainee support** in grants. There should be an opportunity to have students/young investigators as first authors on publications.
- There is a need to have **adequately sample sized follow up studies** (>100,000 subjects) that are **harmonized** through a central organization. It is important to **validate** a large number of new biomarkers. At present, there is no centralized approach to maximize benefit from new biomarkers and the opportunity of doing this work in Canada is limited by its size and diversity of health systems. Each cohort is currently thinking only of its own survival vs. the **need to maximize all resources**.
- There currently exists a gap between individual biomarkers and the application to clinic. There is a need to understand the long haul iterative process of **moving from basic discovery to clinical application**. Biomarker work will create a better understanding of diseases, for example: what individual molecules can teach us about disease process.
- Ability of a group to be organized can be leveraged on **global scale** – e.g. currently ongoing Canadian collaboration with Framingham studies on using similar cohorts and biomarker candidates. This will allow a cross validation with US work. This needs to be amplified with other international collaborations.
- There is an intrinsic **complexity related to pool of biomarkers candidates** to be used for clinical application; there is a need to pick out the most informative candidates so that there is a manageable number that is useful. What is the most effective approach to determine



- this? This question requires biological insight, decision impact prioritisation and clinical validation.
- **Biomarkers standardization** is an important issue that can be done through a **clinical trials repository** for biomarkers studies designed to share cohort data. This implies a need to find a way to standardize quality control. There is also a need to codify the methodologies for biomarker studies and maximize the interface with the clinic in validation and application, with the appropriate ethical safeguards.
 - It was noted that **clinical diversity** is impressive in countries like Canada, we need to address cohort differences in **biomarkers and responses to environmental stressors**. This could potentially give information that would be highly valuable for personalized medicine.
 - There is wealth of research across the country in cohort studies. For example, in paediatrics there is data on collective cohorts that can be accessed through a website. We need to show **who is working on what and specify the various stages of development** for these biomarkers, i.e., creation, diffusion, transformation and use. There is a **need to combine data from across individual studies** when analysing biomarkers. There is also a need to deal with the **ethics and regulatory issues** to facilitate discovery while protecting the patient. CIHR or a central group could take a leadership role in facilitating this.
 - **Collaboration with industry** (particularly in the area of diagnostics) will help build a bridge to clinical application. For example, anit-bnp has still not been used clinically because the cost is still too high. Using the wrong markers could end up being prohibitively expensive.

Following this discussion, the group was provided with an overview on biomarkers from the National Institutes of Health (US) viewpoint.

An NIH Perspective on Biomarkers Discovery and Development

Guest Speaker: Shawnmarie Mayrand-Chung; **Program Director, The Biomarkers Consortium (NIH)**

Dr. Mayrand-Chung began her presentation by discussing the “The Biomarkers Consortium” in the USA, outlining the structure of the organization. There are three founding members of the Biomarkers consortium – NIH, FDA (Food and Drug Administration), and the Pharma Association. The consortium is not government funded; all money comes from the private sector and the NIH fundraising foundation. The consortium is a joint effort on biomarkers designed to share resources and information across all partners.

The aim of the consortium is to facilitate the discovery, development, and validation of select biomarkers using new and existing technologies; help qualify biomarkers for specific applications in diagnosing disease, predicting therapeutic response and improving clinical practice. Its goal is also to generate data useful to inform regulatory decision-making and to make consortium project results - “the biomarker resources” - broadly available to the entire scientific community. It is envisaged that in approximately 5 years there will be a competitive commercialization arm to the organization, allowing profits to be made that can help to support the consortium.

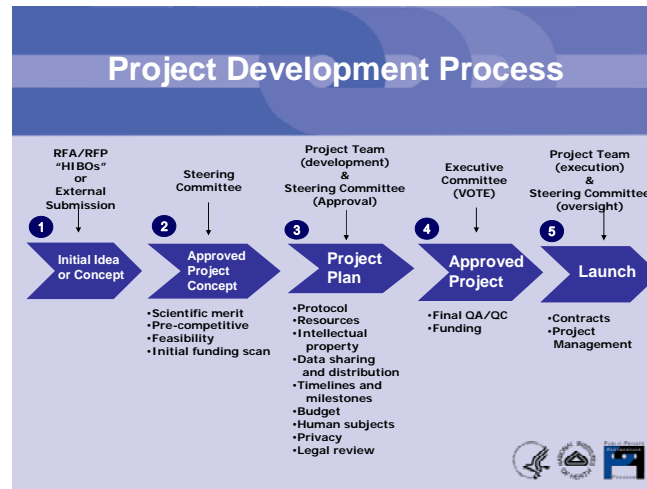
In terms of governance, the three founding members contribute equally and there are representations of all three members in each level of the organization (from the executive

committee through to project teams). For projects, there must also be representation from two different stakeholder groups in each steering committee (as co-chairs).

The consortium works in four areas to date: cancer; inflammation and immunity; metabolic diseases; and neuroscience. It has six key policy areas where the governance, pre-negotiated with the stakeholders (and their legal counsel) representing FNIH, NIH, FDA, PhRMA, CMS and BIO, has been set out to ensure all parties can work together. These include:

- Antitrust
- Confidentiality
- Conflict of Interest
- Intellectual Property
- Data sharing
- Grant Awards / Contractor Selection

The process around project development is five-step and shown below:



In terms of the strategic selection of projects by the consortium, it was agreed to focus on large projects that would distinguish the work from the rest of the biomarker field; it was clear that any project must benefit significantly by being collaborative. The criteria used were:

- **Important:** addresses a significant unmet/scientific need
- **Translational:** will result in significant improvement in the development, approval or delivery of care to patients
- **Transformational:** addresses critical gaps
- **Feasible:** end goals can be likely achieved in a specific timeframe
- **Practical:** leverages pre-existing resources wherever possible
- **Fundable:** is capable of generating the required funding/stakeholder support needed
- **Unique:** not already substantially being done elsewhere
- **Collaborative:** would uniquely benefit from the multi-stakeholder composition and approach of The Biomarkers Consortium

The private sector involvement in funding is important to be able to leverage funds from all sectors involved in biomarker development. This has an added effect of spreading the risk across multiple funders.



There are two types of studies undertaken within the consortium, including (1) retrospective studies (use pre-collected data to mine, analyse and evaluate current biomarkers) and (2) prospective studies (perform biomarker discovery and clinical trials through development). The first completed study was on Adiponectin (a protein hormone produced and secreted exclusively by adipocytes, or fat cells, that regulates the metabolism of lipids and glucose) and this has successfully brought together multiple pharmaceutical companies to work on a single biomarker project. There are currently multiple active projects within the consortium and these range across all levels of biomarker development and all costs (from zero cost, i.e., all in kind contributions, through to multimillion dollar multi-year investments).

Highlights of discussion following the presentation:

- How can the NIH approach be made to work elsewhere?
(A) Need to have increased collaboration across groups involved in biomarkers.
- This is an impressive group brought together with competing interests – how do you ensure inclusion of all kinds of potential subjects (individuals) in projects, for example, the aboriginal community?
(A) As a government organization, there cannot be ‘pay for play’ in selection of subjects to investigate. NIH uses research groups, societies, postings etc. to identify the subject areas that the group addresses.
(B) At this time, no specific criteria is in place to access/include specific populations – there will be a need to put this in place in the future, but not an issue on current projects (e.g. big imaging questions where no benefit to a specific group over another).

Identifying priorities for RFA formulation – World Café technique

The World Café facilitation technique - designed to help groups develop new and innovative ideas through diversity of perspectives and revolving small group discussions - was used to help participants elaborate on key issues and answer the overarching question: What are the major gaps and research opportunities in the area of biomarker research? Nine groups, each focusing on a specific topic, were established and a host was identified to facilitate each of the sessions. Participants had an opportunity to attend three sessions while the hosts remained in the same group, updating each new group on previous conversations and building on the collective information. For the final session, participants returned to their original groups, were updated by their hosts and were asked to summarize discussion, outlining research opportunities as relevant to their topic of discussion. The highlights of discussions from each of the nine groups were summarized and shared with all participants.

Following the World Café, the original groups were reconstituted and asked to identify priorities for an RFA, rating each identified opportunity based on the following criteria: 1. Addresses CIHR Roadmap’s priorities of excellence with global impact; 2. Leverage Canadian strengths where additional funding could make a major difference; 3. Addresses an important gap in knowledge or translation of knowledge; 4. Build appropriate capacity in Canada; 5. Has significant potential to influence health outcomes; 6. Has potentially important economic dividends.

The reports from the nine breakout groups, including the priority rating sessions, are summarized below.



Reports from the World Café and identification of priorities

Group A (Host: Pavel Hamet): 1. What types of biomarkers should be measured? 2. How are the approaches different/same for different disease types or research communities?

Discussion Key Points:

1. *Types of biomarkers to be measured:* Anything useful for screening and diagnosis – the biomarker could be static and/or dynamic. Novel modalities of biomarkers should be sought (Improve over biomarkers that are currently available).
2. *How to approach different diseases?* Research should benefit from having multiple Canadian cohorts. It is important to validate samples that have already been collected (modifying if necessary). Population cohorts are powerful data sets, depicting prevalence of disease in first collection of the cohort. In follow up years, we can get information on incidence cases and validate biomarkers found in the first round. Samples compared from incidence against baseline => improve biomarker with each collection of data.

Other issues identified by the group as related to biomarkers research in different communities included:

- Accessibility of biomarkers
- Characteristics of biomarkers
- Rare diseases (such as Arnold Chiari syndrome or Buerger's Disease) versus common diseases (such as lung cancer or atherosclerosis)
- Multiple predictors of complex disease
- Multi-modal approach ↓ disease → environment → genetics
- Shared versus distinct biomarkers
- Disease as a critical collection of complementary biomarkers
- Interaction across diseases/conditions, e.g. cardiovascular and rheumatoid factor; genetic factors, inflammation, metabolic factors

The following research opportunities were identified as priorities:

1. Consider novel platforms and entities that could serve as biomarkers for clinical application
2. Cross disease comparisons as a strategy to accelerate biomarker development
3. Biomarkers that indicate responses to interventions and predict disease outcomes

Group B (Host: Christoph Borchers): How does one measure biomarkers, and how does one move them onto clinically relevant platforms?

Discussion Key Points:

Research needs to be done through teams, developing tools that could be implemented. Teams need to be multidisciplinary and across the scope of biomarker development and use. It is important to have skilled people to interpret the findings (developing the blackbox). Technology needs to keep



pace with development of biomarker (e.g. need appropriate technology to bring about understanding of the biomarker and the context of the clinical situation).

Some scepticism was expressed around assay noise where there is a subtle difference in patient populations (e.g. in predictive use of biomarkers). There needs to be a balance between sensitivity and utility – more sensitive assays may be more difficult to reproduce, interpret and lead to more false labelling. Strategies should be developed based on what is the best approach to measuring the biomarker. Biomarker platforms should be developed to meet clinical needs.

Description of biomarkers:

- depends on function of biomarkers – diagnostic/predicting
- specific, accurate, sensitive, reproducible and cost-effective
- multiplex – battery of biomarkers
- blackbox technology
- point-of-care – is there a place for it?
- Technology development needs to be integrated

Research Opportunities:

- determine optimal time points – develop, improve and implement. Optimize biomarker context in both laboratory testing and clinical utility
- multi-disciplinary teams – includes clinical perspective
- bring life sciences and physical sciences together (CIHR/NSERC)
- fast track timelines for clinical applications
- There is a great need for more specific assays (more molecular approaches, e.g., moving away from ELISA) even though new assays might be more expensive initially but later save money ... and lives!

The following research opportunities were identified as priorities:

1. Development of innovative biomarker technologies, and enhance reproducibility while maximizing appropriate sensitivity



Group C (Host: Robert Balshaw): What computational tools and skills are necessary?

Discussion Key Points:

The first group began by asking whether the above question is the right one to address as opposed to focusing more on research process. It was agreed that it is important to embed computational expertise in all biomarker projects. Reviews should include statistical review and methodological review. There should also be clear evidence of training for individuals in computational skills (and biology skills for computational scientists). In the context of the cost of data collection, development of computational tools and skills is not a big money item but should be explicitly budgeted, e.g. investigating study methodology – data collection study design, validation design, standard operating procedures (SOPs), measuring and reporting on quality, adaptive trial designs that facilitate the full scope of biomarker development.

Integrating multiple platforms for data created (e.g. large datasets that are anticipated due to multiple emerging technologies) through synthesis, representation, and visualization is important. Also, there is a need for a new approach to reviewing the use of technologies – e.g. systematic reviews of diagnostic test performance. In other words there is a need to build best study designs to encourage effective biomarker development and validation.

Question – how can CIHR facilitate leadership in this area?

- It is not necessary to create large computational projects; simply pulling together working groups on study design can help to build consensus guidelines on approaches to methodology.
- Another potential solution would be to fund a series of workshops with leading computationalists who can compare notes and develop guidelines/suggestions for Canadian researchers (potential collaboration with NIH).
- Alternatively, creation of statistical teams of analysts that can be centralized and spread out across Canada to other groups.

The following research opportunities were identified as priorities:

1. Develop appropriate study methodology and maximize knowledge translation and adoption



Group D (Host: Sean Higgins): How can public health needs and industry needs be concurrently met through biomarker discovery and development (weighing social and economic benefits)?

Discussion Key Points:

There were multiple interpretations of what is meant by different needs of public health and industry. What does public health mean – social and economic components? It was noted that there are difficult ethical issues in collecting data on different populations. For example, there are databanks being developed and used by Statistics Canada – is there any potential for aggregating the multiple cohorts to provide large data sets?

Participants offered the following definitions/interpretations:

Public Needs

- better treatment outcome
- cost effective
- efficiency
- lower toxicity/side effects
- earlier diagnosis
- prevention
- less invasive
- catered to individual
- effective diagnostic
- access to better drugs sooner
- regulatory
- population specific

Industry Needs

- BM test
- reliable
- reimbursable
- resuscitate drug failures
- stratify population
- new drug target
- toxicity markers
- efficacy markers
- surrogate markers
- cost
- drug repositioning
- shorter discovery time
- regulatory

- Need to focus on biomarkers for therapeutic interventions which are a significant cost to the health system. Need to know what the largest cost to the health system is (recommend CIHR fund market study and publish results).
- Need to develop biomarker panels for early detection of multiple diseases. Create a biomarker panel that contains early detection markers that can be used annually to assess individuals.
- It is important to consolidate resources for population based biomarker studies. **Data** – on gene expression arrays, genome sequences, proteomics, biomarker data that can all be collated and modified in a single database. Problem: this has been attempted in Iceland and it was not financially viable. **Cohorts** – try to define a national cohort to be used for biomarkers (e.g. Framingham-esque). Structuring cohorts that exist already so that they can be used in large scale biomarker studies with existing **phenotype information**.

The following research opportunities were identified as priorities (ranked from highest to lowest):

1. Biomarkers for therapeutic interventions which are a significant cost to the health care system
2. Develop biomarker panels for early detection of multiple diseases (screening panel: The Health Canada CHIP)



3. Consolidation of resources (e.g., cohorts, phenotypic data, biomarker data, IT and data solutions) for population-based biomarker studies (accessible centralized data mine / database and IT solution)

Group E (Host: Agnes Klein): How can investigative teams work with regulatory authorities to move biomarkers ahead most effectively?

Discussion Key Points:

Participants identified a series of key research priorities which are further explored below. These include:

- 1) How to build better interaction with regulators (pilot one endeavour) at the Federal and Provincial levels in order to move biomarkers into the health care system better?
 - At provincial level, need to get information on how to move biomarkers into clinical practice setting. This could be achieved by setting pilot centres to initiate the process.
- 2) Ways to improve the understanding on how to file a biomarker (pilot)?
 - Need to learn from other countries and others related fields (e.g. biomarkers used in imaging).
 - Workshops, formal and informal approaches to relationship building.
- 3) Gap analysis of processes required to bridge investigative teams and regulators
 - How and what to file with CADTH/ CDR/ Provinces/ others?
 - Exploratory study (pilot project)
- 4) Centralized regulation and submissions process for biomarker information from satellite research groups.
 - For example, initial biomarker is registered and other following biomarkers from satellite groups are 'fast-tracked'

The following research opportunities were identified as priorities (ranked from highest to lowest):

1. How to file a biomarker submission to validate the biomarker (criteria - ready to go to the clinic)
2. Centralized submission for biomarkers

During the Open Discussion, it was enquired whether Health Canada can be involved in research projects as research partners. A. Klein mentioned that representatives from Health Canada can be advisors but usually are not part of the research group; if there is no apparent conflict, Health Canada can nominate researchers.



Group F (Host: Fiona Millar): 1) Why does research into biomarkers fail to translate into clinical practice? 2) How can new, effective biomarkers make it expeditiously into the health care system?

Discussion Key Points:

Q1. The failure of translation arises, first, from the challenge of developing usable biomarkers that have a realistic opportunity to become medical tests.

Problems are several-fold: There are systemic problems with bio-libraries and bio-repositories related to the quality of samples and information about them that limit the potential of biomarker discovery. In addition, those engaged in biomarker research and development often lack clarity regarding what might be characterized as the “architecture of clinical utility” – that is, an understanding of the kind of biomarkers that might warrant uptake, from a clinical and organizational perspective (e.g. there may be a market for theranostic biomarkers for cancer, but less of a market for prognostic biomarkers). There is also a lack of clarity regarding the translational pathway for biomarkers. Improved understanding of the regulatory process is often helpful relatively early in the translational research process; some suggested a role for “knowledge brokers” in facilitating awareness.

Q2. The failure of translation also arises from the challenge of uptake of validated biomarkers.

Problems are several-fold: There is often insufficient evidence regarding clinical utility and cost effectiveness to warrant investment. However, even when available evidence clearly demonstrates the clinical and economic effectiveness of a new biomarker-based medical test, there are challenges with (i) the adequacy of mechanisms for technology assessment in the diagnostics domain, (ii) funding mechanisms for medical tests (e.g., to pay for a theranostic when a drug is covered, to replace or supplement outdated tests), (iii) equipment and organization issues to generate medical test results (e.g., lab information systems, adequate lab capacity and expertise), and (iv) service delivery issues for medical tests (e.g., ordering behaviour, interpretation and effective use among front-line clinicians).

The following research opportunities were identified as priorities (ranked from highest to lowest):

1. Health services and policy research on biomarkers
 - Looking at systems of assessment and delivery of biomarker technology.
 - Looking across jurisdictions to see if there is learning that can apply to biomarkers.
 - Generating evidence regarding the clinical and cost effectiveness of promising biomarkers.
2. Bio specimen science
3. Systematic reviews for biomarker science
 - synthesize evidence of technology platforms, disease domains etc to better identify gaps and opportunities.



Group G (Host: Mark Loeb): How are observational and other clinical trials set up to evaluate biomarker utility, and how can biomarker solutions be sought more consistently in accompaniment of therapeutic clinical trials?

Discussion Key Points:

Two themes emerged from the discussions: a Retrospective theme and a Prospective theme.

For the Retrospective theme, it was mentioned that investigations could be encouraged to leverage existing **cohort studies with well established phenotypic** and biobank data (e.g. CVD studies in Canada). To support this, CIHR needs to support the establishment of an inventory of such cohort studies with biomarker-research potential, which would include information on the breadth of data and biobanked samples. In addition, there is also a need to figure out resources available to Canadian researchers – e.g., industry trials that allow secondary questions to be addressed within a specific trial. In other words, how can one use industry trials to investigate biomarkers? Complementing these resources would be an inventory of different groups working on biomarker research.

For the Prospective theme, investigations could be encouraged to piggy-back biomarker questions on other research questions. For example, **prospective cohorts would be very useful to piggy back on existing cohorts outside biomarker studies** (to collect info and biobank data) – although there will be a need to include the cost of biobanking in proposals for those studies.

A successful Biomarker research initiative will need a foundation of informed research approaches, research policy and programs that deal with the complex issues of biobanking, e.g., ethical issues, jurisdictional differences, and long-term storage. CIHR should support the establishment of a ‘consortium’ of researchers working on established phenotypes to collaborate with CIHR and other funding agencies on addressing issues of biobanking specimens. To expand on some of these:

- There is an opportunity to link administrative databases in health care to biobanks – i.e., link phenotype to biobank information. Jurisdictional issues will need to be considered (e.g., SARS and need for national jurisdiction).
- There are constraints on timing and the related ethics approval. Can one continue collecting data after funding has finished or will one need a new ethics approval?
- There is a need in the field of biomarkers to create a collaborative spirit to increase the art of the possible. There will continue to be a need to coordinate the biomarker groups across the country

For RFA purposes, it will be important to add among the evaluation criteria the requirement of demonstrating that standard operating procedures (SOPs) are in place for assessing biomarkers. This procedure will ensure that biomarkers that are being studied are also valid.

With respect to study design promoted in the RFA, there should be no constraints on biomarker study design although investigators can get credit for using existing resources (e.g. existing biobank data). It was deemed important that there be existing evidence for the biomarker in question.

There is a need to focus on large studies but also need to look at translational studies prior to performing full cohort studies (feasibility studies). There are logistical and feasibility issues that are beyond the scope of an RFA, and it will be necessary to find out how to address these issues.



A question surfaced around biological plausibility – how do you establish biological plausibility? There will continue to be a need for pilot work, focusing on biomarkers with high risk/high reward. Funding of pilot projects with a focus on new technologies and new thinking, for example, are still needed.

Two final questions surfaced which remained unanswered: how can we make biomarkers better industry sponsored and how do we go about creating a more robust peer review process in biomarker research?

Finally a cautionary note was provided: It is important to note that there are systemic variables that must be contemporarily dealt with.

The following research opportunities were identified as priorities:

1. Large scale studies: clinical trials or observational studies
2. Pilot Project (experimental or technical)

Group H (Host: Peter Liu): What is/are Canada's niche(s) in regards to biomarkers? What priorities are there for each of the clinical specialties or disciplines?

The following research opportunities were identified as priorities (ranked from highest to lowest):

1. Multidisciplinary training of future leaders in “personalized health care”
2. Consortium to fast track validation and application of new biomarkers and technologies
3. Use health system research to identify impact on practice and outcomes, and barriers in biomarker utilization
4. Link and coordinate Canadian cohorts with quantitative standardization to identify and validate disease biomarkers

Note: 3 and 4 received same ranking

Canada's opportunities(s) in regards to biomarkers:

There is a need to create impact through better integration. We need to build on exiting strengths including:

- System biology platforms – CFI, Genome Canada, CIHR
- Cohorts
- Biobanks
- Clinical trials, networks with global leadership
- Bioengineering innovation

The research opportunities in this area should focus on how to:



1. Fast track biomarker discovery to validation to application
2. Validate new technologies in a clinically relevant context
3. Link and standardize cohort data/samples

There is uniqueness in Canada in that while we do have a single publically funded health care system, we really have at least 14 subsystems. As a result, we have the ability to track and monitor outcomes and drug utilization patterns across jurisdictions and compare this to the unique features of the individual population. It is as though Canada has a national experiment across each of the health systems (10 provincial, 3 territorial and at least one federal).

Research Opportunities should also include:

1. Evaluation of the barriers and uptake of biomarkers into practice, and impact on practice and outcomes
2. Cost effectiveness modeling and evaluation of biomarkers in the health system

Because of Canada's ethno-cultural diversity, our large geography and environmental diversity there are multiple sub-populations that can be studied using biomarker research.

Research Opportunities include:

1. Unique biomarkers for risk, prognosis or treatment response in subpopulations?
2. What are the priorities for each disease disciplines?
3. Research into topics within each discipline where the largest impact will likely be made

It was recommended that while general strategies exist for biomarker research across the disciplines, each discipline should also allow the degrees of freedom to foster innovation in addressing urgent clinical needs to maximize research impact (e.g. cost-effective tailored therapy in cancer or arthritis, or prognostication in lung disease). On the other hand, there is a need to maintain a very wide stakeholder group to synergize the solutions to the challenges of biomarkers.

Multidisciplinary collaboration and networking is important to build international leadership in disease networks. Canada is just "large enough, but small enough" to have an impact here. It will be important that there are technological interfaces with clinical teams. There is a need to research how to:

1. Build consortium linking centres and networks together for biomarker translation
2. Foster future leadership in interdisciplinary "personalized health care" experts

Group I (Host: Ron Heslegrave): How can ethical considerations be handled well for potential subjects, for researchers, for the private sector, and for others?

This group had a lively discussion about ethics and biomarkers. It was noted that ethics should be placed early in the continuum of biomarker research (i.e. through the full process of biomarker development).

There was a debate over how to provide feedback to cohorts. It can be difficult to decide what is appropriate. With biomarkers, most of the work does not provide data that is informative to the



patient but rather it is more of clinical value to the patient. This seems to fit with traditional models of diagnostic services. There is opportunity to address new ethical issues that may arise from biomarkers – e.g. surveillance of individuals providing biomarker data. Issue over specific biomarker data that isn't yet clinical but will be, implies a need to have an ethical system in place in order to allow research to continue when there is more 'heat' over ethical issues around biomarkers. Some parts of ethics system are in place, but there is neither an actual strategy nor system for Canada.

The group agreed that to develop a long term ethics strategy for cohorts a number of issues will need to be addressed, including:

- Do we need policy guidelines practice? (ethics of biomarker)
- Is the biomarker predictive for survival?
- Framework for the ethical evaluation of biomarkers.
- Issues of data access and control up front in the process (ethical consideration).
- Ethics consideration at the point of Research Ethics Board (REB) is too late.
- Ethics should be included in the design of trials.
- Consider regulations oversight for biomarker testing.
- Issues of conflict of interest for framework (REB involvement, IP, etc.).
- How do we get multi-institutes involved?
- Develop mechanisms to ensure that marginalized groups are not forgotten (i.e. rare disorders).
- The way biomarker research is integrated into clinical trials.
- Building on what has already been done (share information).
- Governance access of data (i.e. vulnerable populations).
- Relevant to human health (not just clinical disease).
- How do we communicate to people what we know about their biomarker profile?
- What are the ethical obligations ten years from now? Need clear framework to deal with this.
- Create mechanisms to keep registries up to date (but we need to apply existing principles).
- Establish new best practices; best practices might be different at each stage.
- Capacity building (culture of ethics).
- Allow bioethicists to apply for funding.
- Build bioethicists into scientific teams.
- There needs to be a bioethics core to the RFA.
- Address consent issues at extremes of life.
- Bioethical principles vs. bioethical validation.
- The notion of "difference" and how humans perceive this.
- Look at doctor-patient relationship models; how best to translate information into patient care.

The following research opportunities were identified as priorities (ranked from highest to lowest):

1. Streamlined ethics oversight processes
2. Building an ethical framework for biomarker research
 - Understand how to move forward on privacy, consent, and other issues. There is a need for consistent reporting and sharing of data/ specimens across jurisdictions. How to deal with current regulatory structure? Need to include ethics in developing cohorts and data collection/analysis.
3. Ethical gap analysis regarding biomarker lifecycles



• There may be different ethical issues at different points in the development process – may need to ask different ethical questions at different points. Capacity building around this issue is needed.



Final Words and Next Steps

Peter Liu briefly summarized the second day of the workshop. It was reiterated that training, ethics, and computational opportunities need to be considered when drafting an RFA. It will be important to find the most innovative and feasible approach to funding that can move the biomarker work forward. There is a hope to create a biomarker community through this initiative.

Below is a summary of the overarching themes for a forward going research agenda:

- **A better understanding of the current biomarker landscape.** It is clear that there is a lot of work being completed in Canada across the lifecycle of biomarkers research. It is critical that a catalogue of information be created that will identify what is being done, what stage of development/application each biomarker is in, who is doing what, and the timelines for each initiative.
- **Building capacity.** There is a need to build capacity and leadership across members of the biomarker teams. This could take on the form of workshops, mentorship programs, communities of practices and formal training.
- **Defining roles and processes.** It is important to increase understanding of the regulatory process and find ways to involve the private sector early in biomarkers research and development. Better processes will help move biomarkers research from discovery to diffusion to transformation and eventually their use in clinical practice.
- **Leveraging the knowledge of all members of the biomarker ‘team’.** To expeditiously move biomarkers from the bench to the bedside, it is essential that the knowledge, skills and judgement of team members are utilized fully at all stages of the process. Bringing ethicists, regulators, clinical biochemists, chemists, engineers, physicists, clinicians, health services and policy researchers, and computationalists into the process early and regularly will help not only identify key issues that need attention but also figure out valid solutions.
- **Collaboration across Institutes, granting councils, jurisdictions and countries.** Although biomarkers research is sometimes associated with high risks, it is important to keep in mind that it also has the potential for large rewards. Working with team members with a diversity of skills, experiences and methodologies will help uncover and mitigate risks early and increase the likelihood that success is plausible. It may be time for CIHR to take on the lead in creating an integrated network of biomarker researchers that can deliver on the mandate of excellence and partnerships with others – crossing Institutes, granting councils, jurisdictions and country boundaries.
- **New research methods and data linkages are required to support biomarkers research.** Not every biomarker will be a success and produce return on investment. Thus, it is essential that new tools and methods be developed to reduce the risks and increase the capacity of the health system to take up new biomarkers. Some suggested approaches that are worth exploring include: systematic reviews, meta-analyses, large scale clinical trials, adaptive trial designs, logic models, new computational and statistical approaches, cost-benefit analyses, and regulatory impact analyses. In addition, to support biomarker research excellence and maximize efficiency, it is essential to find ways to consolidate various data sources such as biobanks and ‘piggy back’ on existing data/studies such as those led by Statistics Canada and the Canadian Longitudinal Study on Aging.
- **Development of new technologies and platforms.** It is important that new technologies and technological platforms be created and used in Canada. Technological innovation is necessary and some might even say a necessary evil. Canada has traditionally been a laggard in the development and uptake of new technologies when compared to other



countries. We are fortunate to be proximal to a neighbour who does not share this view. Canada needs to continue to invest in appropriate technology where it can show additional economic and social value. Finding the comfort zone of decision makers on how much to invest in risky technological ventures is no easy task but is necessary.

In summary, it is critical to the future of the biomarker community to build a culture of excellence that incorporates quality research, innovation, research translation, risk sharing, entrepreneurship, interdisciplinary collaboration and partnership among stakeholders. The culture must be built on a better understanding of the current biomarker landscape that includes recognized gaps and opportunities. The development of a common registry, building capacity, knowledge mobilization, and the development of new methods and platforms are all important issues to tackle to further biomarkers success in predictive and precision medicine.

This national workshop has brought together diverse expertise from multiple research fields, institutions and sectors to work collaboratively and contribute to the development of new initiatives at CIHR. The issues, gaps and opportunities in the biomarker field that the workshop participants identified will form the foundation for developing successful programs in partnership with multiple stakeholders. It is our hope that these new initiatives will lead to major advancements in biomarker discovery, development and implementation, having distinctive impact on human health.

APPENDIX 1 – Please see WORKSHOP BOOKLET for detailed program



APPENDIX 2

Biomarkers Workshop - Evaluation Results		
General	Topic/Session	Feedback (out of 5)
Goal 1	To examine the current state of knowledge re: the realm of biomarkers related to more precise healthcare interventions, reaching from prevention through to management of advanced stages of disease	4.44
Goal 2	To deliberate and advise about the most important themes related to biomarkers wherein programmatic funding could move the field forward in Canada, especially in niche domains where we can compete and contribute distinctively	4.04
Goal 3	To discuss and prioritize the best funding vehicles to use in offering a Request for Applications to the Canadian Health research community	3.05
Goal 4	To develop the framework for a Request for Application on the topic of biomarkers for better human health	3.71
Workshop Proceedings		
1. a)	Plenary Session I: The Personalized Healthcare Imperative - Where Biomarkers Fit	4.45
b)	Respondents and moderated discussions	3.88
2. a)	Plenary Session II: Quality Measurement of Biomarkers	4.43
b)	Respondents and moderated discussions	4.05
3. a)	Plenary Session III: Taking Biomarkers from Discovery to the Clinic	3.9
b)	Respondents and moderated discussions	3.83
4	Dinner presentation: How do Biomarkers systems biology and better medical care connect? Sergio Baranzini	4.19
5	Presentation: An NIH Perspective on Biomarkers Discovery and Development - Shawnmarie Mayrand-Chung	4.52
6. Breakout Groups		
A	What types of biomarkers should be measured? How are the approaches different/same fore different diseases types or research communities?	4
B	How does one measure biomarkers, and how does one move them onto clinically relevant platforms?	3.57
C	What computational tools and skills are necessary?	4.5
D	How can public health needs and industry needs be concurrently met through biomarker discovery and	3



	development?	
<i>E</i>	How can investigative teams work with regulatory authorities to move biomarkers ahead most	1.5
<i>F</i>	Why does research into biomarkers fail to translate into clinical practice?	3.33
<i>G</i>	How are observational and other clinical trials set up to evaluate biomarker utility and how can biomarkers solutions be sought more consistently in accompaniment of therapeutic clinical trials?	4.14
<i>H</i>	What is/are Canada's niche/s in regards to biomarkers?	4
<i>I</i>	How can ethical consideration be handled well for potential subjects, for researchers etc...?	4
7	Report back from Breakout groups	3.95
8	Moderated Open Discussion and Key Elements of the RFA (priority setting)	3.2
9	Final Reflections	4.1
Overall		
1	How would you evaluate this workshop as a learning experience?	4.39
2	Do you feel you were given enough opportunity to provide feedback and contribute to the priority setting exercise?	4.27
3	3) How useful was the meeting package and background material?	4.04
4. a)	4) a. Workshop booklet - Do you feel the one page summaries provided you with useful background information about biomarkers research in various fields?	3.52
b)	b. Do you think reviewing the one page summaries helped you think about multi-disciplinary research as related to biomarkers?	3.45
5	5) What is your overall satisfaction with the workshop?	4.43
6	6) How would you evaluate the overall organization of the workshop?	4.24
7	7) How would you evaluate the overall program?	4.33
8	8) Did you find the participants list and contact information useful?	4.38