Ontario has high quality health technology assessment (HTA) processes through such agencies as OHTAC, CADTH, CED, pCODR and others. These agencies seek to apply the principles of evidence-based medicine coupled with cost-efficacy analysis to make recommendations about health interventions to the health care system and to government funding agencies. However, personalized medicine technologies present some particular challenges to the current HTA process that must be addressed to ensure continued efficacy of such agencies. Failure to adjust to these challenges will impact not only the uptake of health interventions, but also the flow of Ontario research findings into the clinic, and the development of the biotechnology industry in Ontario.

**WHAT IS THE PROBLEM?**

Personalized medicine (PM) is a healthcare model based on the use each patient’s molecular characteristics to better inform clinical decisions. PM technologies have the potential to better diagnose a patient’s disease, guide treatment, and even predict disease onset and guide prevention. However, such technologies have not had the anticipated impact on patient health or on industry success (Crawford and Aspinall, 2012). Problems include the fact that payers have resisted uptake due to unclear clinical utility and cost effectiveness, and clinical labs struggle with regulatory issues, payment and with rapidly changing technologies. This impacts entities such as the Ontario Health Technology Assessment Committee (OHTAC) in its efforts to insure that PM technologies are implemented based on evidence and with an understanding of the cost implications.

Challenges to the HTA process specific to personalized medicine technologies include:

- Genetic polymorphisms in drug metabolizing and other genes contribute to drug toxicity and their use has the potential to improve patient response while reducing health care costs, yet few such pharmacogenetic tests have entered routine clinical use. There is an urgent need to better understand how to evaluate the clinical utility, health impact and cost effectiveness of pharmacogenomic testing for drug toxicity given the negative impact on health outcomes.
- Test cost such as those for genomic sequencing have dropped to the point that individuals are paying for such tests themselves. This creates pressure to react to the results in the absence of appropriate validated information, or to adopt unproven technologies (either through public or private payers). This in turn creates un-wellness, anxiety and unmet expectations to which the public system will have to respond.
- Changing clinical trial structure – While the randomized controlled trial is the traditional gold standard for establishing clinical utility, the use of a companion diagnostics complicates
interpretation (how does one distinguish between the clinical utility of the test from that of the drug or the drug/test combination). There is also the fact that targeted diagnostics are designed for specific subsets of the population for which the use of a randomly-chosen patient pool might render the trial inconclusive and even inappropriate. New clinical trial modalities are being tested. For example, the recently FDA-approved drugs crizotinib and Vemurafenib (plus respective companion diagnostics) were approved based only on data from two single-arm studies.

- Companion diagnostics present a range of challenges. Such diagnostics are exemplified by trastuzumab to treat patients whose tumours carry the Her2/neu fusion gene, or tamoxifen for tumours expressing the estrogen receptor. Given that the cost of targeted therapeutics can be expected to increase as the potential patient pool shrinks (e.g. a reported $300,000/year for the cystic fibrosis drug Kalydeco, specific for about 4% of the CF population), this makes the use of companion diagnostics imperative. The HTA challenges with respect to companion diagnostics include:
  - As mentioned above, the need to develop approaches to reviewing clinical trial data where the trial included the use of a companion diagnostic
  - The current OHTAC/HQO process for evaluating technologies includes estimates of cost-effectiveness, but new genetic technologies present rapid changes in analytical capability which is influencing the cost and quality control of companion diagnostic tests. Also the current distribution of test amongst different sites lacks coordination, complicating quality control and access. From the perspective of the HTA process this will impact cost utility analysis
  - The cost of the companion diagnostic may not be included in the overall cost-effectiveness ratio calculation. For example, the industry provider of the associated therapeutic often pays for (or is forced to cover the cost of) the companion diagnostic. This complicated the HTA process.
  - Just as companion diagnostics will identify patients most likely to benefit, these will, by definition, identify patients unlikely to benefit. However there are challenges in withholding a treatment, particularly if there are few other options. Consideration may need to be given towards evaluating the (lack of) efficacy of a treatment in the non-indicated population.

- Genetic tests for inherited diseases have implications not just for the patient but that patient’s existing family and future progeny. As an example, hypertrophic cardiomyopathy (HCM) is the leading cause of sudden death in young athletes but is typically asymptomatic until a catastrophic presentation occurs. There are many contributory genetic markers to HCM that could be used to avoid costly routine monitoring of family members; however it is not yet possible to confidently predict outcomes for those with the mutation. Those with the mutation might avoid healthy physical exercise unnecessarily. Scenarios such as this make determining the cost efficacy difficult.
• Drug companies will be unwilling to define responsive patients for drugs already on the market given that this will likely reduce the target population. Private funding will be needed to evaluate off-patent drugs. HTA systems may be challenged by insufficient data in such cases.

• For both patented and off-patent drugs, HTA processes might also be challenged when considering termination of coverage when there might be a (not apparent) responsive subpopulation. Decisions based on whole population analysis might be challenged.

WHAT IS THE DESIRED OUTCOME?

• A transparent HTA process for all PM technologies as already demonstrated e.g. by OHTAC, MOAC, who publish their terms of reference, committee members, and technology assessment reports
  o Transparency reinforces evidence-based decision making,
  o Need accessible information on why a technology will be supported, and equally important, why a particular technology will not be supported.
  o This gives system resilience when public opinion favours a particular treatment when the evidence is against its use

• The efficient use of HTA resources during assessment of PM technologies; to avoid use of inefficient or inappropriate HTA tools

• To take full advantage of cost savings opportunities for the health care system

• A reliable and structured approach to laboratory testing. This will not only facilitate the HTA process itself by enabling better cost estimates and more rapid uptake, but will have much broader impact on access, quality and cost efficiency. This is of particular importance to the application of companion diagnostic testing.

• To improve current state of awareness for patients, health care systems and health care providers of evolving best practices regarding PM these technologies. The current level of awareness lags significantly.

• Faster uptake of Ontario inventions via an efficient HTA process, which in turn will inform and guide the pre-market development of technologies by Ontario researchers and industry; this will enhance the growth of the Ontario biotechnology industry

The overriding objective is the efficient integration of PM technologies into the health care system supported by appropriate evidence-based and cost effectiveness analysis to better serve Ontario patients.

WHAT ARE THE BARRIERS?

As identified above there are some specific challenges to evidence-based review of personalized medicine technologies yet there is no specific ways to address them outside the population screening (Maternal Child Screening Committee of PMCH) or oncology (MOAC) contexts.
RECOMMENDATIONS

- Within the context of current HTA bodies in Ontario, develop the ability to address areas of exception and additional need in the existing HTA-cost utility framework precipitated by new personalized medicine
  - Examine how MOAC’s methodology can be used outside cancer
  - Prepare a guide for OHTAC/HQO in its assessment of marketed PM technologies; potentially add new case studies added as they become available to illustrate new points.
  - Pay particular attention to companion diagnostics, LDT tests
    - Coordinate discussions with CADTH and pCODR regarding their discussions of these topics
    - Consider other jurisdictions, and in particular consider Australia which has made significant progress in this area
- Provide a better receptor capacity by a more structured approach to laboratory testing - while not a component of the HTA process, there are significant deficiencies that threaten the delivery of appropriately quality controlled genetic testing, which in turn impacts the HTA process. Of particular concern are tests that are not provided as licensed kit (which is controlled by Health Canada) that are developed independently amongst the different genetic laboratories. This raises the concern of quality of testing. This is coupled with disparity of funding plus the problem that there is little/no coordination of what test is offered where, leading to possible inequity of access. The excessive cost and potential low quality will hamper the HTA process.
- Improve our ability to validate PM tools. Establish databases for the collection of large amount of data and the development of bioinformatic tools to evaluate this data relative to disease processes. The challenge will be to find meaning amongst the complexity of chronic disease development and complex population variation.