Minimal Residual Disease (MRD) Evaluation in Childhood ALL: A Health Policy Analysis

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By:
Nicole Bradley, MHSc
Senior Healthcare Analyst & Project Manager
Pediatric Oncology Group of Ontario (POGO)

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Response to Therapy for Pre-B ALL: MRD

Issue Identification: Ensuring Access to MRD Evaluation

• Priority arising from POGO’s long-range plan and stakeholder consultation, Provincial Pediatric Oncology Plan (PPOP) 2011 Status Update

• Minimal Residual Disease (MRD) is:
  – a prognostic test used to:
    ▪ predict risk of relapse; and
    ▪ determine best course of treatment
  – considered standard of care in treatment of pediatric leukemias.

• MRD testing for Ontario patients has occurred in US reference laboratories

• MRD funding for pre-B ALL via NCI by virtue of enrolment in COG clinical trials
  – Anticipated to cease, necessitating a plan for its continued availability

• Repatriate future testing to Ontario (forward planning, optimize identified efficiencies and build capacity)
POGO Response

• Assembled POGO MRD Working Group (2012), consisting of multidisciplinary, provincial experts, including:
  – Pediatric Oncologists
  – Hematopathologists/ Laboratory Technologists/ Lab Managers

• Objectives of POGO MRD Working Group:
  – To identify current, evidence- & consensus-based standard of care indications for MRD
  – To generate a provincial plan for equitable access to MRD for identified indications in Ontario labs
  – To develop a case to support MRD lab activity in Ontario for pediatric precursor-B ALL.

• Consulted with peers regarding success factors in obtaining lab test funding in Ontario, including:
  – Cancer Care Ontario (CCO)
  – Provincial Programs Branch and Laboratory & Genetics Branch, MOHLTC
  – Health Quality Ontario (HQO) re: provincial health technology assessment (HTA) process via *Ontario Health Technology Advisory Committee (OHTAC)*
Highlights of POGO MRD Working Group Activity

• Created a clear statement of the component issues, including:
  – valued added to patient outcomes and system efficiencies and capacity;
  – potential obstacles to testing in Ontario; and
  – probable time of occurrence.

• Established Task Forces to develop components of a business case for funding
  – MRD Optimal Lab Criteria Task Force
  – MRD Standard of Care Task Force

• Developed consensus-based lab standards/ criteria for repatriating MRD to Ontario labs for pre-B ALL
  – E.g. validation and ongoing quality assurance, critical volumes, sample handling/turnaround time, and lab access

• Endorsed standard of care indications\(^1\) for optimal use & timing of MRD, developed based on:
  – Landmark publications from contemporary ALL and AML trials
  – Standard of care survey amongst nine clinical trial consortium leaders in N. America and Europe (including COG, DFCI, SJCRH, UK ALL & BFM)

POGO MRD Working Group
Standard of Care Recommendations

**Pediatric ALL**
- Baseline (diagnostic) sample
- **Day 8** after start of induction therapy in peripheral blood
- **End of induction** (“**day 29**”) in bone marrow
- **End of consolidation** (*for patients with positive MRD at end of induction*)
- **During end of re-induction** (*for patients with intermediate risk relapsed ALL*)
- **Prior to proceeding to hematopoietic stem cell transplant (HSCT)**

**Pediatric AML**
- Baseline (diagnostic) sample
- **End of first course of induction therapy** *on all newly diagnosed patients*

Highlights of POGO MRD Working Group Activity (continued)

• Evaluated lab capacities and test volumes to ensure critical mass

• Generated annual MRD testing volume and cost estimates for bringing testing to Ontario
  – In collaboration with POGO system and health analysts, based on POGONIS data and literature-derived assumptions

• Achieved consensus on optimal number of labs to perform the test
  – Based on anticipated provincial MRD sample volumes & critical mass

• Prepared and submitted a request for an arms-length HTA to OHTAC, in collaboration with POGO (accepted and prioritized, August, 2015)

• Supported the process carried out by OHTAC by providing clinical content expertise
Health Technology Assessment (HTA) 101

• “A multidisciplinary field of policy analysis [that] studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology.” (INAHTA 2016)
  – Including: drugs; prognostic, diagnostic and screening tests; surgical/medical devices and procedures; and broad health system issues. (INAHTA & CADTH, 2016)

• Provides evidence-based information for decision making and priority setting to a range of stakeholders
  – e.g. health care providers, hospital administrators, health system/policy planners/decision makers)

• Decision determinants framework used to generate funding recommendations includes:
  – Overall Clinical Benefit — clinical effectiveness, safety, burden of illness, and need
  – Value for Money — economic evaluations
  – Societal Values — consistency with expected (or demonstrated) societal and ethical values
  – Feasibility of Adoption into Health System — economic and organizational feasibility

CADTH – Canadian Association for Drugs & Technology in Health; INAHTA – International Network of Agencies for Health Technology Assessment
### HTA Process

#### Scoping
- HQO drafts brief overview of intervention
- OHTAC determines which interventions proceed to full review

#### Evidence-Based & Cost Analyses
- HQO reviews evidence in consultation with:
  - Clinical experts and/or expert panels
  - Scientific partners
  - Industry
  - Government

#### Draft OHTAC Recommendations
- OHTAC drafts recommendations based on evidence-based analysis
- Occasionally OHTAC’s recommendations include a request for a field evaluation in instances where there is uncertainty regarding the existing evidence

#### Professional and Public Consultation
- Draft review and recommendations are posted on the HQO website for public and professional comment

#### Assessment of Comments
- HQO reviews public and professional comment feedback
- OHTAC modifies recommendations as necessary

#### Post Review and Recommendation
- HQO evidence-based review and OHTAC recommendations are approved by HQO Board and published on the HQO website

#### Appeal – N/A
- Following the final posting of HQO Board-approved OHTAC recommendations, any person may submit an appeal within 60 days

#### Field Evaluation – N/A
- If OHTAC has recommended a field evaluation (and that recommendation has not been appealed), a study would be conducted to assess effectiveness and cost-effectiveness of an intervention in the Ontario context
- Field evaluations are typically recommended when there is uncertainty regarding the existing evidence

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http://www.hqontario.ca/evidence/evidence-process/evidence-review-process
www.HQOntario.ca
OHTAC Recommendation  
(March, 2016)

“The Ontario Health Technology Advisory Committee recommends publicly funding minimal residual disease evaluation for pediatric management of acute lymphoblastic leukemia.”


Current Status

- Ontario has developed capacity for MRD assessment via two labs
- COG deadline for funding cessation extended
  - to ensure adequate capacity for MRD in labs across North America
- Implementation planning for transition of MRD assessment to Ontario via:
  - development of provincial MRD sample flow pathway to facilitate new/optimal referral patterns and ensure critical volumes are met/maintained
  - further clarification and specification of sample handling and lab access parameters
  - development of tools (supportive documents, standardized forms) to support sample flow, sample submission and associated billing
- Continued POGO–MOHLTC discussions re: provincial MRD funding support
Lessons Learned

- Established, high-quality HTA processes in Ontario via existing agencies
  - Interdisciplinary, transparent, arms length and accessible
  - Provides system resilience in adoption of effective and efficient technologies
  - Increasing efforts to incorporate meaningful patient advocate/societal input

- Challenges of current HTA systems in evaluating pediatric technologies
  - Limitations re: evaluation of pediatric evidence
    - Current gold standard (Phase III RCTs) not always possible or available
  - Balance between effectiveness, efficiency, equity, societal & ethical values
    - How can the framework incorporate unique aspects of special populations? In different health system contexts?
    - Individual or population lens?
    - Whose values should be considered? Patients? Healthcare Providers? Policymakers? Society?
Lessons Learned
(continued)

• Other considerations re: HTA
  – Rapid rate of change in era of personalized medicine/ targeted therapies –
    timeliness of HTAs
  – Efficient use of HTA resources for technologies of relatively rare diseases?
  – Inclusion of critically important patient outcomes (eg. EFS)
  – Uptake of HTA recommendations in health system funding decisions/
    implementation may be variable (Menon, et al, 2009)

• A nimble, responsive, timely pediatric specific HTA adapted process is
  needed, based on:
  – levels of evidence considered reasonable for pediatrics;
  – expert content input; and
  – consideration of societal and ethical values pertaining to children as distinct
    from other populations

• Building lessons learned into future policy analyses/ discussions
  – Current POGO long-range planning activities, PPOP 2017-2022
Thank you!

The contributions of the following are appreciated:

- **POGO MRD Working Group**
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- **Dr. Sandy Nuttal**, Director, Strategic Projects, POGO
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Provincial MRD Working Group (2012–2016)

POGO Executive Lead
Dr. Corin Greenberg
Chief Executive Officer, POGO

Working Group Co-Chair
Dr. David Malkin
POGO Medical Director & POGO Chair in Childhood Cancer Control

Working Group Co-Chair
Dr. Mohamed Abdelhaleem
Division Head, Haematopathology, & Director of Molecular Haematopathology, Hospital for Sick Children (SickKids)

Working Group Co-Chair
Dr. James (Jim) Whitlock
Chief, Division of Haematology/Oncology, Hospital for Sick Children (SickKids)

Working Group Member
Dr. Uma Athale
Pediatric Hematologist/Oncologist, McMaster Children’s Hospital, Hamilton Health Sciences (MCH, HHS)

Working Group Member (2012–2014)
Dr. Ronald Carter
Director, Laboratory Genetic Services, Hamilton Regional Laboratory Medicine Program

Working Group Member
Dr. Paul Gibson
Pediatric Hematologist/Oncologist, Children’s Hospital, London Health Sciences Centre (LHSC)

Working Group Member
Dr. Johann (Hans) Hitzler
Section Head, Leukemia/Lymphoma, Hospital for Sick Children (SickKids)

Working Group Member
Dr. Donna Johnston
Chief, Division of Hematology/Oncology, Children’s Hospital of Eastern Ontario (CHEO)

Working Group Member
Mr. Mike Keeney
Coordinator, Hematology/Flow Cytometry, London Health Sciences Centre (LHSC)

Working Group Member
Dr. Elaine Leung
Head, Division of Haematology & Transfusion Medicine Program, Children’s Hospital of Eastern Ontario (CHEO)

Working Group Member (2015 – present)
Dr. Elizabeth McCready
Head, Molecular Cytogenetics, Hamilton Regional Laboratory Medicine Program, Hamilton Health Sciences & St. Joseph’s Healthcare

Working Group Member
Dr. Michael Rauh
Hematopathologist, Kingston General Hospital (KGH)

Working Group Member (2015 – present)
Dr. Catherine Ross
Pathologist, Juravinski Hospital & Hamilton Regional Laboratory Medicine Program

Working Group Member
Dr. Luke Shier
Hematopathologist, Ottawa Hospital & Director of Clinical Flow Lab, Eastern Ontario Regional Laboratory Association (EORLA)

Working Group Member
Dr. Mariana Silva
Division Head, Pediatric Hematology/Oncology, Kingston General Hospital (KGH)

POGO Support
Ms. Nicole Bradley
Senior Healthcare Analyst & Project Manager, POGO