

Assessing the value of diagnostic innovation: A growing role for HTA?

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Institute of Health Policy, Management & Evaluation
UNIVERSITY OF TORONTO

Panel overview

- Blockbuster diagnostics?
 - Fiona Miller, Stuart Hogarth, Kelly Holloway
- Assessment of diagnostic tests prior to introduction in Québec
 - François Rousseau
- Assessing the value of diagnostic innovation at HQO
 - Irfan Dhalla
- The CADTH experience
 - Tammy Clifford
- Q&A

Disclosures

- No COI to declare

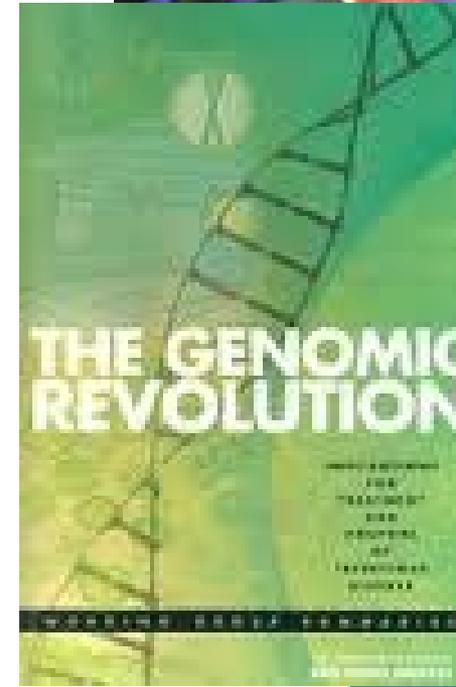
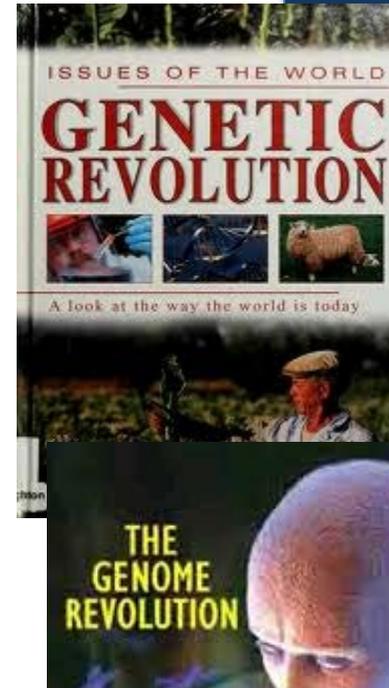
Blockbuster diagnostics

A GROWING CHALLENGE?

High expectations - Science

- “Today, one of our biggest goals is to cut the cost of sequencing an entire human genome to \$1,000 or less ... leading to a **revolution in the practice of medicine**. ... I expect that within the next decade or so, most people living in developed nations will have their genomes sequenced as part of their medical record ...”

Dr. Francis Collins, NIH Director,
Yale Journal of Medicine and Law April 2011
Emphasis added



High expectations - Industry

“Roche Diagnostics is pioneering the expansion of diagnostics to encompass all stages of healthcare, to include predisposition testing, screening and prevention.

This proactive approach is designed to enable a shift from cost-intensive, acute care to individualised, preventative medicine.”

Roche Diagnostics publicity material,
November 2004

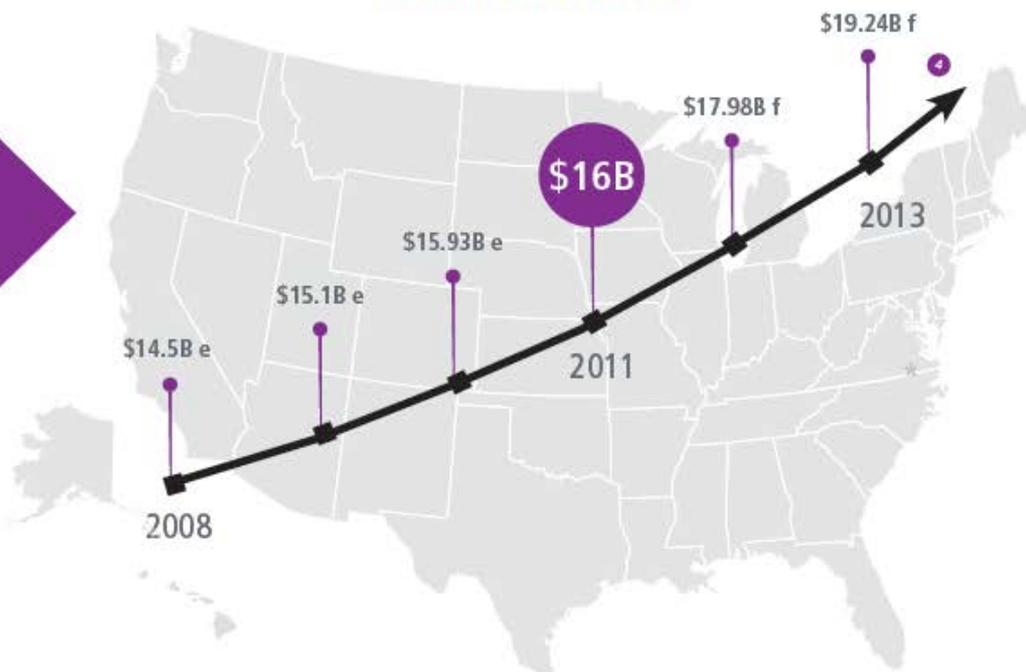
Heino von Prondzynski, Roche Diagnostics, Paris, 2004

The global in vitro diagnostics (IVD) industry

GLOBAL DIAGNOSTICS MARKET



U.S. DIAGNOSTICS MARKET



Source: AdvaMedDx

In vitro diagnostics (IVD) prices

Old business model

Test	Price
Thyroid	\$28
HIV	\$13
Pap Smear	\$8
Prothrombin	\$6
Urinalysis	\$5

New business model

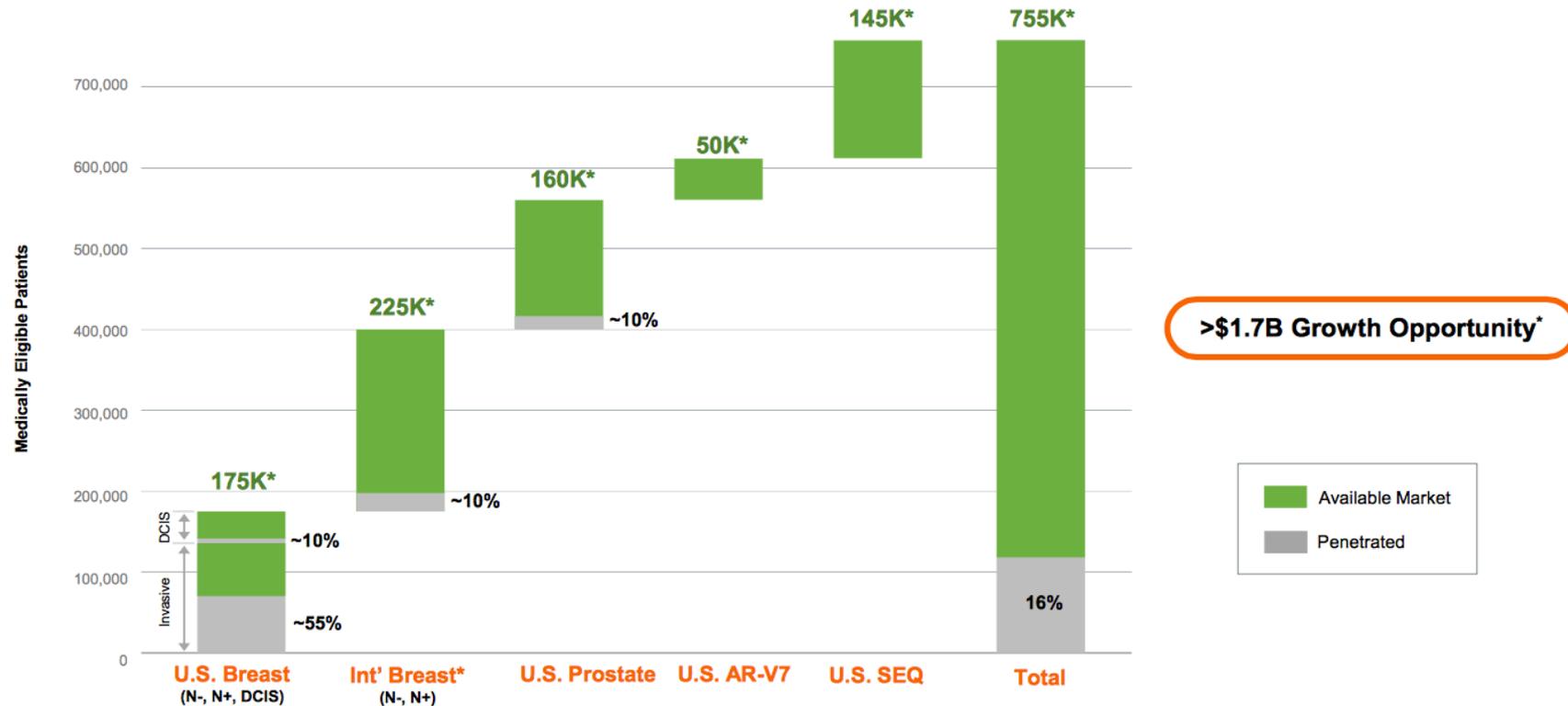
Firm / molecular test	Price
Veracyte / Afirma	\$4,875
Agendia / MammaPrint	\$4,200
Genomic Health /Oncotype Dx	\$4,175
AssureRx / Genesight	\$3,800
CareDx/ AlloMap	\$2,821

An example: Oncotype Dx

- Available in Canada since end-2007
 - Media reports 10,000 – 15,000 Canadian women have used the test
 - Funded by most provinces
 - Ontario - 2010
 - Quebec - 2010
 - Saskatchewan – 2012
 - Newfoundland - 2012
 - BC – 2014
 - Alberta – 2014
 - Nova Scotia - 2016

Genomic Health – Investor presentation, 2017

Double Digit Growth Opportunity with Currently Marketed Tests



* Management estimate based on 2016 market size and average selling price.

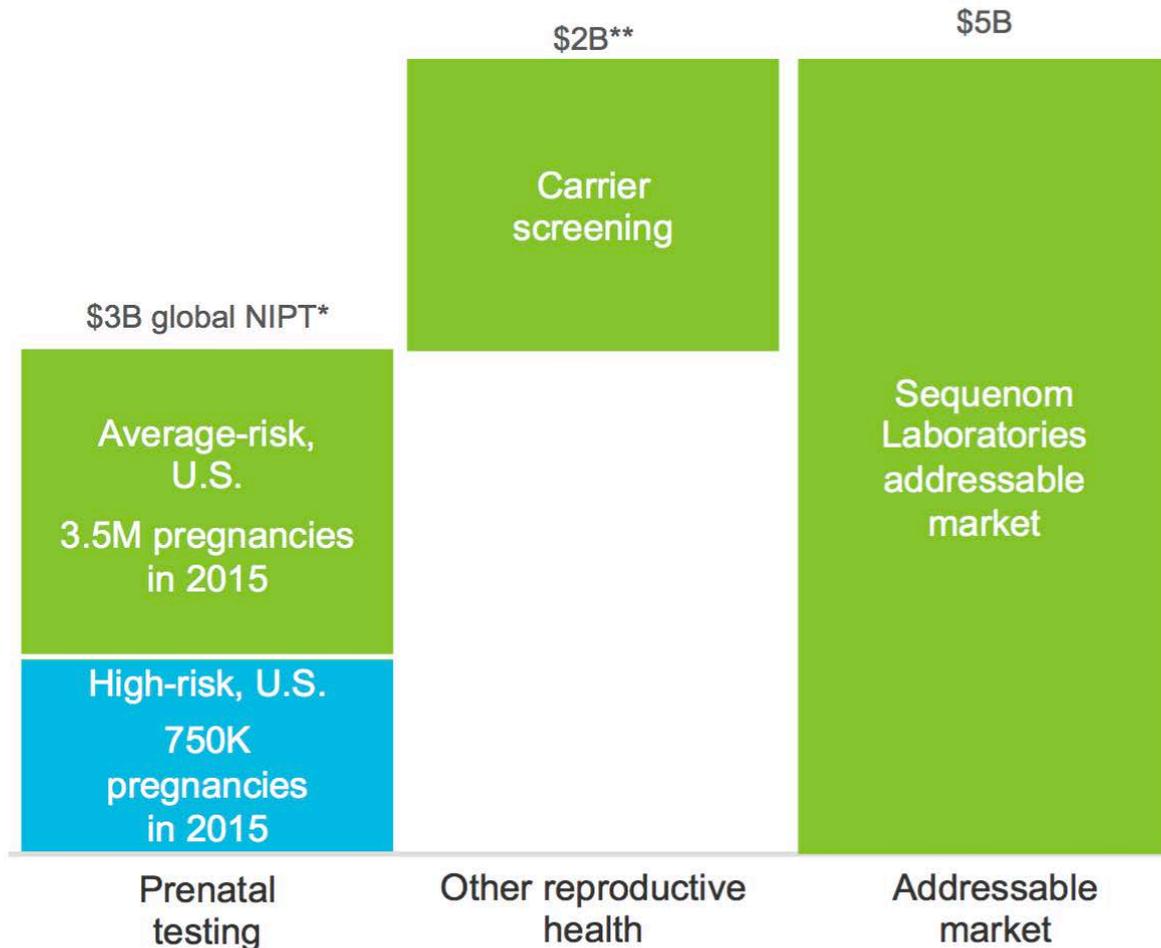
** 7 Key OUS Markets

An example: Non invasive prenatal testing

- Multiple commercially available “non invasive” prenatal screening tests available globally since 2011
 - Global market estimated at \$3.62 billion in 2019
 - Cost varies - \$550 CAN (Lifelabs, Patient Pay) to *\$2900 US (billed to insurers, Sequenom)
- Coverage in Canada (second tier test)
 - Ontario – 2015
 - BC – 2015
 - Manitoba
 - Nova Scotia

Sequenom – investor presentation, 2016

Reproductive health worldwide: \$5B by 2020



Diagnostic innovation

LOW BARRIER TO ENTRY?

MIT Technology Review

Biomedicine

Theranos Promised a Revolution, but Delivered Dangerous Errors

FDA orders genetics company 23andMe to cease marketing of screening service

Agency is 'concerned about the public health consequences of inaccurate results from the PGS device'

is  

The New York Times

SUBSCRIBE

LOG I

RESEARCH

How Bright Promise in Cancer Testing Fell Apart

More harm than good?

Use of genetic mental health tests has grown rapidly. But evidence they work is scant.

Beth Daley | New England Center for Investigative Reporting

Market access regulation - Limited

- Medical device regulation is weak relative to drug regulation
 - Many IVDs classed as “low risk” and attract limited regulatory attention
 - Low burden of proof for access to the market
- Many other tests bypass statutory regulation altogether
 - The Laboratory Developed Test (LDT) loophole
 - A “Regulatory black hole” (Patsner, 2009)

What is an LDT?

- “an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory.” FDA, 2014
- “devices that are manufactured and intended to be used in a professional and commercial context for purposes of medical analysis without being marketed“ EU IVD Directive (Art 1(6))
- “Reagents, instruments, apparatus, equipment or systems not manufactured, sold or represented by manufacturers for use in in vitro diagnostic applications are not considered to be IVDDs. This includes many products sold for general laboratory applications, even if they are used by laboratories to develop their own diagnostic assays for the laboratory's own use ("Laboratory Developed Tests" [LDTs]).”(Health Canada, 2016)

FDA & Laboratory Developed Tests

- LDTs subject to US Federal Food, Drug & Cosmetic Act
 - FDA has generally exercised enforcement discretion
 - “The FDA has generally not enforced premarket review and other applicable FDA requirements because **LDTs were relatively simple lab tests and generally available on a limited basis**. Due to advances in technology and business models, LDTs have evolved and proliferated significantly since the FDA first obtained comprehensive authority to regulate all in vitro diagnostics as devices in 1976. **Some LDTs are now much more complex, have a nationwide reach and present higher risks**, such as detection of risk for breast cancer and Alzheimer’s disease, which are similar to those of other IVDs that have undergone premarket review.”
 - (FDA, Laboratory Developed Tests, last updated 01/13/2017; <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/default.htm>, Accessed April 13, 2017; emphasis added)

FDA & Laboratory Developed Tests

- FDA have intervened on ad-hoc basis
 - Warning letters to industry/ Safety alerts to public
- FDA moved to oversee LDTs; then a retreat
 - 2010 - Public Workshop on LDT regulation
 - 2014 - LDT draft guidance
 - 2015 - Public Workshop on LDT regulation
 - 2017 – Discussion paper on LDTs “to simply advance the public discussion”

EU & Laboratory Developed Tests

- LDTs have not been subject to active oversight
- New IVD regulation increases oversight of all diagnostics (passed 2017; to take effect 2022)
 - New risk classification system
 - More tests subject to premarket review
 - Greater emphasis on clinical evaluation
- Significant closure of LDT loophole
 - Exemption for LDTs put into service in health institutions, but not for “devices which are manufactured **on an industrial scale** and which are used within the framework of a commercial diagnostic service.”
 - Draft new regulation (Para 15 of Recital), emphasis added

Health Canada & Laboratory Developed Tests

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An example: Oncotype Dx

- LDT performed in Genomic Health's clinical lab
 - Redwood City, California
- Not approved by the US FDA, Health Canada, etc.
 - “**⚠️⚠️⚠️**This test was developed and its performance characteristics determined by Genomic Health, Inc. **It has not been cleared or approved by the FDA, nor is it required to be.** The laboratory is regulated under CLIA as qualified to perform high complexity testing.” <http://breast-cancer.oncotypedx.com/en-CA/Professional-Invasive/Ordering/ReadingTheReports/Node-NegativeReport>

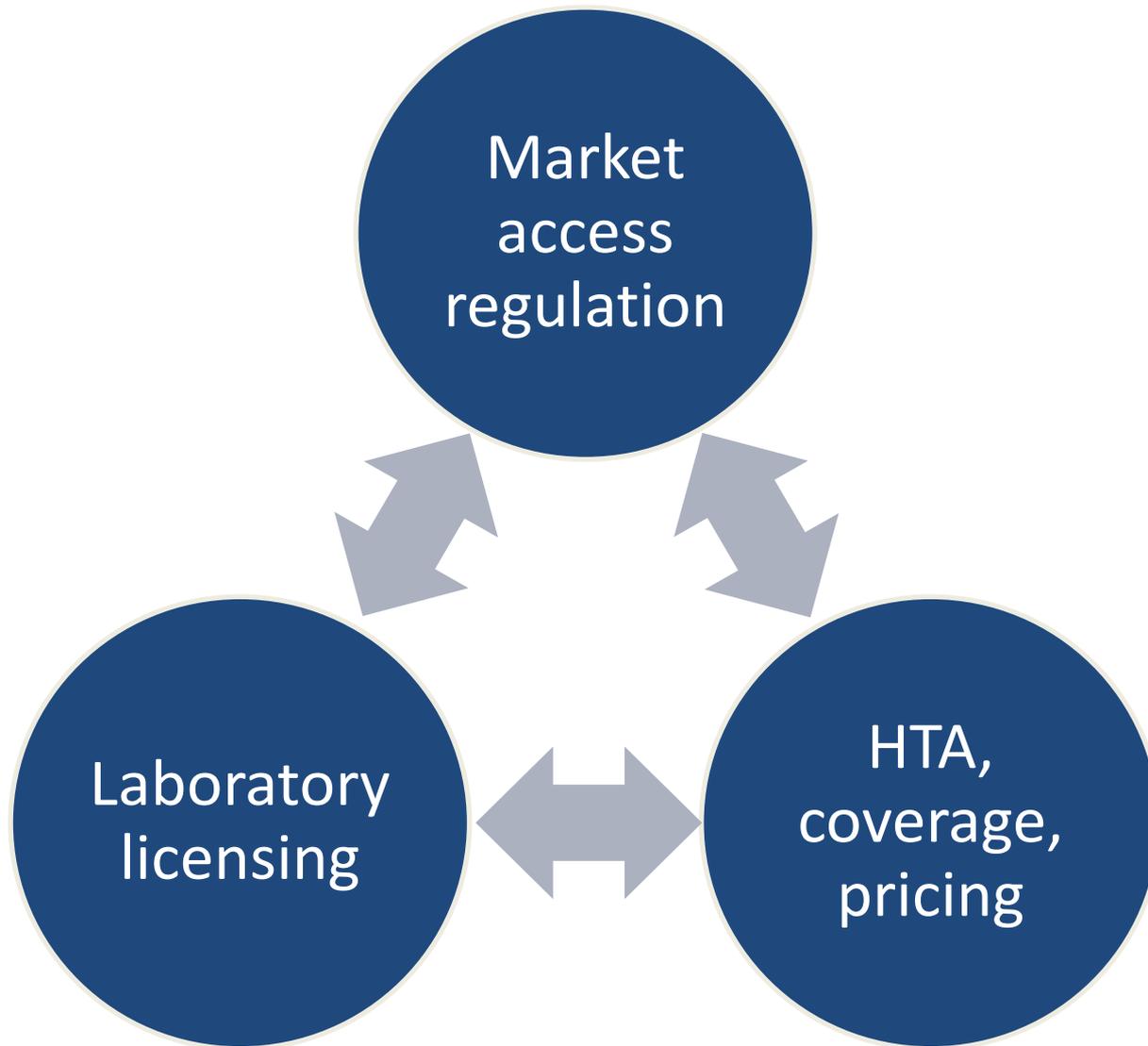
An example: Non invasive prenatal testing

- LDTs – performed in multiple laboratories
- Not approved by the US FDA, Health Canada, etc.
 - Ariosa – licensed to and available through Dynacare labs across Canada
 - “*The Harmony Prenatal Test is developed by Ariosa Diagnostics. Ariosa Diagnostics is a laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA). **As with other laboratory-developed tests, this testing service has not been cleared or approved by the US FDA or any other federal regulatory agencies.**” (<http://www.ariosadx.com/about-us/>)
 - Natera – licensed to LifeLabs, based in Toronto
 - Natera, Inc. The test described has been developed and its performance characteristics determined by the CLIA-certified laboratory performing the test. **This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA).** Although FDA does not currently clear or approve laboratory-developed tests in the U.S., certification of the laboratory is required under CLIA to ensure the quality and validity of the tests. (<https://www.natera.com>)

Adoption and diffusion of diagnostics

A GROWING ROLE FOR HTA?

Polycentric regulation



Growing HTA interest in diagnostics?

- UK, NICE Diagnostics Assessment Programme
 - Since 2011, completed guidance for 26 topics
 - 17 IVD; 5 imaging; 4 other
 - 9 in process (6 IVD; 3 other)
- Canada
 - Quebec
 - INESSS Committee on Scientific Evaluation of Laboratory Tests
 - Ontario
 - Molecular Oncology Advisory Committee, CCO
 - No cost effectiveness
 - Genetic Testing Advisory Committee, MOHLTC (to 2016)
 - No cost effectiveness
 - Ontario Genetic Advisory Committee, HQO (from 2017)
 - ?

Acknowledgements

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Stuart Hogarth, Cambridge University

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“Blockbuster diagnostics” Team

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CIHR



Colleagues at THETA



*Assessing the Value of Diagnostic Innovation:
A Growing Role for Health Technology Assessment?*

Assessment of diagnostic tests prior to introduction in Québec

**CADTH Symposium
Ottawa - April 25th 2017**

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Déclaration d'intérêts

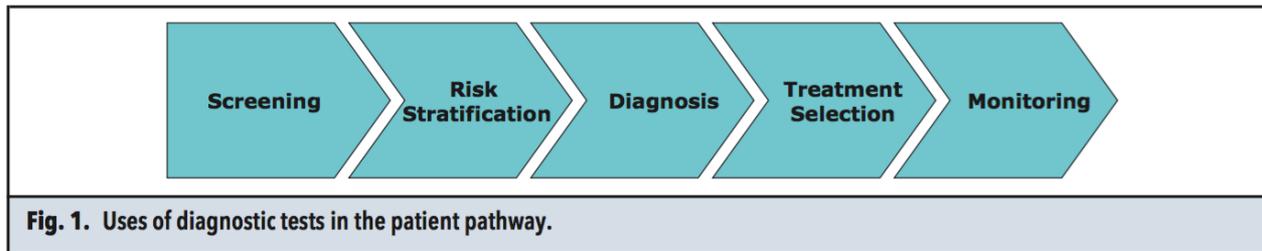
- ◆ Aucun financement/rémunération direct du privé
- ◆ Co-financement en nature (Génome Canada):
QIAGEN, LifeTechnologies, Perkin-Elmer, Illumina,
Ariosa Dx
- ◆ Aucune participation à comité avisé de
compagnies privées
- ◆ Financement public par les Instituts de recherche
en santé du Canada, FRSQ, Genome(s)



Clinical Laboratories in Canada

- Population 35 millions (2013);
- ~ 670 millions diagnostic tests / year (2015); ~ CAN\$ 3 B
- 6-7% of hospital expenditures;
- Estimated to be involved in up to 70% of all medical decisions;

Review



Hallworth et al. Clinical Chemistry 61:4 Review 589–599 (2015)

What does it takes for a test to work ?

- The test must **measure** what it is supposed to measure (*analytical validation*);
- The test result must correctly **classify patients** (*clinical validation*);
- Classification of the patients must lead to **improved health outcomes** (*clinical utility*);
- The whole process must fit into the health care **budget** (*economic evaluation*);
- Ethical, social and legal **acceptability**.

HTA

To add a new laboratory test offer in Québec a hospital lab needs approval by the Ministry of Health.

Otherwise no resources for this test will be made available to the lab offering the test.

Process in place since 2012 and implies formal HTA.

Mécanisme d'évaluation des procédures de biologie médicale à l'INESSS

Process for introducing new clinical tests in Québec

New test proposal

INESSS Eval Committee

AJOUT AU RÉPERTOIRE (Nouvelle analyse)

Consultation auprès de l'INESSS – mécanisme permanent d'évaluation des nouvelles analyses de biologie médicale au Québec :

- mode régulier
- mode urgence si requis

INESSS

- Évaluation et recommandation d'ajout ou de refus d'introduction au Répertoire au ministre (*incluant l'examen et la délibération du comité scientifique d'évaluation des analyses de biologie médicale*)
- Délai maximal de trois mois
- Mécanisme de demande urgente disponible si requis

MINISTRE

- Décision de refus ou d'ajout ou de maintien d'une analyse au Répertoire
- Avis transmis à la DBBM

MSSS - DGSSMU

Si analyse acceptée :

- Création de codes au Répertoire
- Désignation d'un ou de plusieurs laboratoires producteurs
- Attribution des ressources et organisation des services

AJOUT AU RÉPERTOIRE

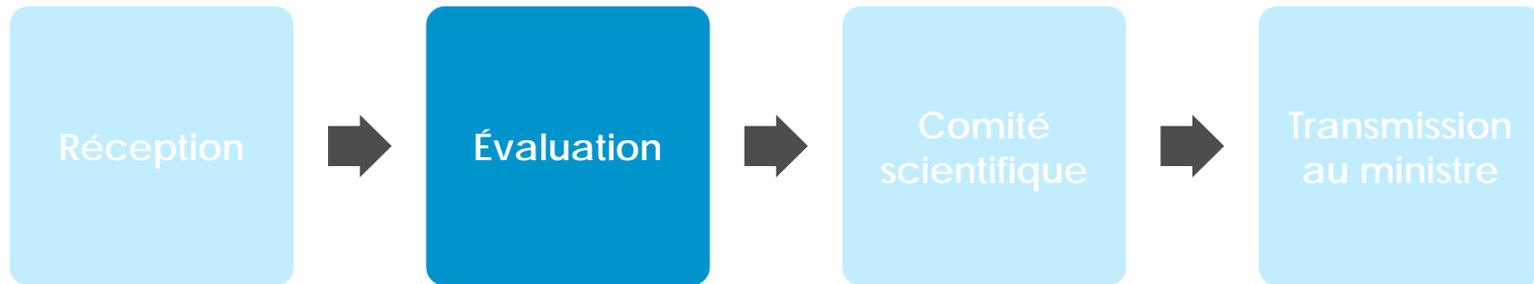
- Publié annuellement sur le site du MSSS (1^{er} avril)
- Mise à jour du Répertoire des analyses suprarégionales sur le site Web : <http://www.msss.gouv.qc.ca/repertoires/biomed/>

Submitting a new test to the Ministry of Health

Standard Form with the following information:

- Details on test identification : Name, description of the assay, main indication, assay method, homologation status/validation status, cost per test
- Details on intended use: targeted patients, relevant disease(s), relevant medical specialties (users), algorithm of use, clinical information needed
- Details on test provider: who will be responsible for test, sample trajectory (needs to be 100% clinical grade), turn around time, local expertise
- Evidence base (citations) for: Clinical utility, clinical validity, analytical validity
- Quality control plan (internal, external)
- Expected clinical need: tests/year, prevalence & Incidence of targeted diagnosis, impact of new test on current standard of care, existing guidelines.

Évaluation



- Évaluation des analyses de biologie médicale par l'INESSS :
 - mars à septembre - juillet à décembre - novembre à mai
- Les analyses de *biologie médicale* sont évaluées par des professionnels scientifiques de l'INESSS.
- L'évaluation est notamment appuyée par les critères suivants :
 - la pertinence clinique (bénéfices pour la santé);
 - la validité clinique (exactitude avec laquelle une analyse identifie une affection clinique);
 - la validité analytique (robustesse du test);
 - différents enjeux spécifiques (organisationnels, éthiques, économiques, etc.).

Évaluation des analyses de biologie médicale

Dimension

Définition

Composantes

Utilité clinique

Le degré avec lequel les bénéfices sont conférés par des résultats pour le patient, positifs ou négatifs.

- Disponibilité des interventions et leur impact
- Bénéfices et risques sur la santé

Validité clinique
(Performance diagnostique)

Une mesure de l'exactitude avec laquelle une analyse identifie ou prédit une affection clinique.

- Sensibilité clinique
- Spécificité clinique
- Valeur prédictive positive
- Valeur prédictive négative

Validité analytique
(Capacité technique)

Un indicateur de la capacité d'une analyse à mesurer la propriété ou la caractéristique que l'on entend mesurer.

- Sensibilité analytique
- Spécificité analytique
- Fiabilité (précision, exactitude)
- Robustesse de l'analyse (c-à-d., la résistance aux petits changements dans les variables analytiques)

Enjeux économiques

Les coûts du recours à l'analyse de biologie médicale dans la perspective du système de santé québécois.

- Analyse d'impact budgétaire
- Coût/efficacité

Enjeux organisationnels, éthiques, professionnels, juridiques et sociaux

Enjeux liés à l'analyse et pouvant affecter l'organisation des soins de santé, les personnes, leur famille ou la société.

- Modalités d'implantation des tests
- Changement de processus de soin

The ACCE framework

Box 5. Biomarker clinical evaluation: Definitions

The ACCE Model Project (an initiative of the CDC's Office of Public Health Genomics, OPHG) developed the first publicly-available analytical process for evaluating scientific data on emerging genetic tests. The ACCE Model Process identified four main criteria for evaluating a genetic test:

- **Clinical validity** describes the accuracy with which a test predicts a particular clinical outcome; when a test is used diagnostically, clinical validity measures the association of the test with the disorder; when used predictively it measures the probability that a positive test will result in the appearance of the disorder within a stated time period.
- **Clinical utility** is the likelihood that using the test result will lead to an improved health outcome; to evaluate this, the important information is about the effectiveness of the interventions available for people who test positive and the consequences for people with false positive or false negative results.
- **Analytical validity**, a component of clinical validity, describes how accurately and reliably the test measures the genotype of interest.
- **Ethical, legal and social implications (ELSI)** refer to other implications which may arise in the context of using the test and cross cut across the clinical validity and clinical utility criteria.

Source: Centers for Disease Control and Prevention (n.d.)

Table 1 Key features considered by payers in implementation of the three-part framework

Level of analysis, EGAPP nomenclature ¹ (IOM nomenclature ²)	Representative aspects of the payer’s analysis
Analytical validity (analytical qualification)	<p>Methodology for the test’s implementation (e.g., different molecular strategies may measure the analyte; different manufacturers’ kits may vary in analytical performance; different protocols may measure different lists of mutation sites)</p> <p>Test metrics at the level of clinical chemistry–chemical sensitivity (e.g., ng/ml), robustness to chemical interference (chemical specificity), precision</p> <p>Robustness under expected clinical specimen handling conditions (“preanalytical” processes)</p> <p>Robustness when implemented in different regional laboratories</p>
Clinical validity (clinical validation)	<p>Define the population(s) used to standardize the test</p> <p>Define expected future populations with whom the test may be used</p> <p>Clinical metrics that associate analytical test results with clinical parameters (response or nonresponse to a drug; prognostic accuracy for cancer relapse; the likelihood of adverse drug events)</p> <p>Discuss if and how clinical validity metrics derived from prior study populations could shift for the intended future population (spectrum shifts)</p>
Clinical utility (utilization)	<p>Describe the test’s impact on patient care in a defined scenario (for a defined population; for a defined pending decision), relative to alternative approaches to the patient’s care</p> <p>The payer will evaluate incremental test utility against reasonable clinical alternatives for the defined clinical scenario (e.g., watchful waiting; response to therapeutic trial; serum drug levels in lieu of advance pharmacogenetic testing)</p> <p>The payer will weigh cost and number-needed-to-test considerations, as balanced by likely savings</p> <p>The payer will weigh uncertainties presented by the risk of unnecessary or difficult-to-control utilization</p>

Payers will look to test developers or commercial test providers to provide data or rationales that address the issues shown. The examples in the table are representative, not exhaustive.

The GETT framework

Clin Chem Lab Med 2010;48(10):xxx-xxx © 2010 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2010.291

Development and description of GETT: a Genetic testing Evidence Tracking Tool

International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) – IFCC Scientific Division Committee on Molecular Diagnostics

François Rousseau^{1-3,*}, Carmen Lindsay^{2,3}, Marc Charland^{2,3}, Yves Labelle³, Jean Bergeron^{1,3}, Ingeborg Blancquaert^{2,4}, Robert Delage⁵, Brian Gilfix⁶, Michel Miron⁷, Grant A. Mitchell^{1,2,8}, Luc Oligny^{1,8}, Mario Pazzagli^{2,9}, Cyril Mamotte^{2,10} and Deborah Payne¹¹ on behalf of the IFCC Scientific Division Committee on Molecular Diagnostics

¹ Réseau de Médecine Génétique Appliquée du Fonds de Recherche en Santé du Québec, Québec, Canada

² The CanGèneTest Research Consortium on Genetic Laboratory Services (www.cangenetest.org), Québec, Canada

clinical applications still lag behind expectations, partly due to the lack of effective tools to systematically search for and summarize published data relative to the clinical assessment of new diagnostic molecular tests.

Methods: Through a collaborative process using published tools and an expert panel, we developed a detailed checklist of the evidence that needs to be collected or produced to evaluate the potential usefulness of a new molecular diagnostic test. This tool is called GETT, for Genetic testing Evidence Tracking Tool.

Results: GETT allows 1) researchers to summarize the current evidence and to identify knowledge gaps for further research and: 2) stakeholders to collect data related to a given



A Research and Knowledge Network in Genetic Services and Policy
Un réseau de recherche et de connaissance sur les services et politiques de santé en génétique

78 countries



Characteristics and definitions of themes and sub-themes of GETT.

1 Overview of the disease: epidemiology and genetics

1.1 Disease prevalence

1.2 Disease outcomes

1.3 Clinical management and treatment

1.4 Costs associated with disease

1.5 Pattern of inheritance

1.6 Genetic heterogeneity

1.7 Mutation prevalence

1.8 Mutation penetrance

1.9 Neomutation rate

2 Diagnostic tools

2.1 Approaches other than molecular

2.1.1 Methods

2.1.2 Analytical validity

2.1.3 Clinical validity

2.1.4 Infrastructures and costs

2.2 Molecular approaches

2.2.1 Methods

2.2.2 Analytical validity

2.2.3 Clinical validity

2.2.4 Infrastructures and costs

2.2.5 Interpretation

2.2.6 Consensus or best practice guidelines

3 Quality improvement program

3.1 Internal

3.2 External

4 Clinical utility

5 Screening or diagnostic strategies

6 Impacts on the health care system

6.1 Foreseeable needs for testing

6.2 Costs (including replacement of existing analyses, cost/effectiveness and cost/utility studies)

6.3 Tests accessibility

6.4 Availability and accessibility of professional services, health care and follow-up, expertise and training

7 Psychological and social aspects of the analysis

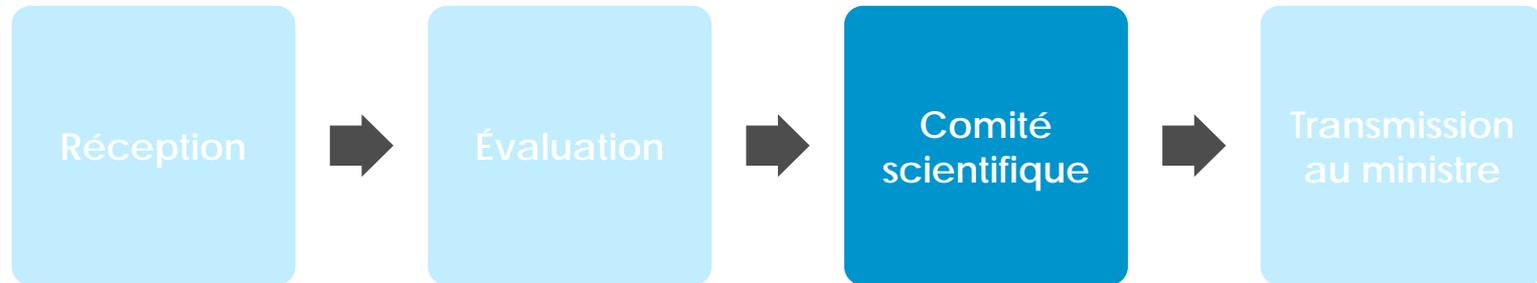
8 Ethical and legal aspects of the analysis

9 Synthesis

10 Research priorities

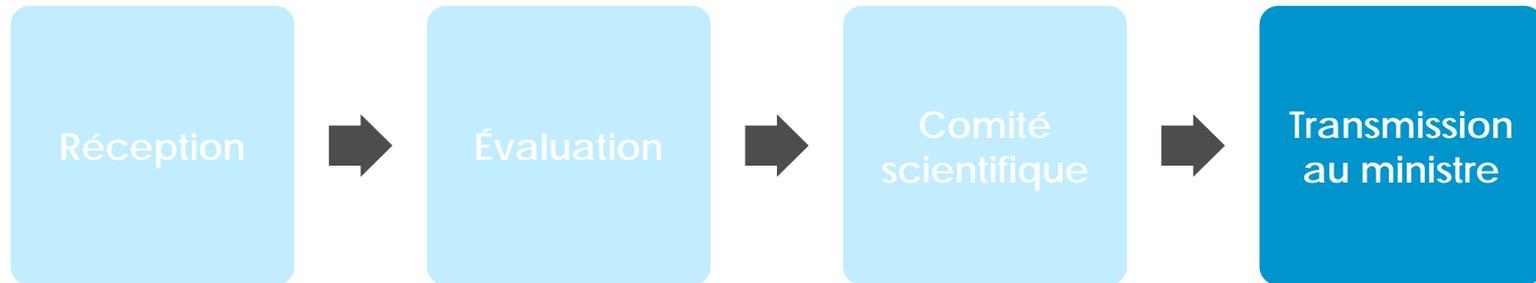


Comité scientifique des analyses de biologie médicale



- Composition du Comité scientifique
 - Hématologue
 - Biochimiste clinique
 - Médecin biochimiste
 - Pathologiste
 - Microbiologiste infectiologue
 - Généticien
 - Pédiatre
 - Éthicien
 - Membre citoyen

Transmission des recommandations au ministre



- Les recommandations sont entérinées par le président-directeur général de l'INESSS et transmises au ministre.
- **Les recommandations avec le dossier complet sont rendues publiques**
- Le ministre approuve ou non les recommandations de l'INESSS concernant la mise à jour du *Répertoire*.

Transmission des recommandations au ministre

Secteur	Introduction/ Maintien	Intro/condit.	Réévaluation	Refus	Total	% Acceptées
Biochimie	8	3	2	13	26	42 %
Génétique	15	2	10	3	30	57 %
Hématologie	24	4	7	5	40	70 %
Microbiologie	12	0	1	3	16	75 %
Pathologie	0	1	0	0	1	100 %
Total	59	10	20	24	113	61 %

Sept 2016

In the case of LDTs



- *Analytical validity* of test:
 - Little or no data on LDT's analytical validity is published (proprietary information);
 - We do not see the same rigor in validation of LDT across laboratories;
 - Usually no independent proficiency testing program (and no reference method!);
 - Cannot assume same performance from lab to lab;

Laboratory developed tests (LDTs) : there are guidelines

MM17-A
Vol. 28 No. 9
Replaces MM17-P
Vol. 27 No. 21

Verification and Validation of Multiplex Nucleic Acid Assays; Approved Guideline

This guideline provides recommendations for analytic verification and validation of multiplex assays, as well as a review of different types of biologic and synthetic reference materials.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.



CLSI MM17-A

Analytical validation of laboratory test ?

Characteristic of test	ISO terminology
It must work as well as other validated methods	Accuracy Method comparison studies
It must detect the sample characteristic sought for (when present)	Analytical sensitivity /Limit of detection/gDNA input range
It must not detect other things as being the characteristic sought for	Analytical specificity Interferences Sampling contaminants Cross reactivity
It must always give the same result for the same sample	Precision Repeatability Reproducibility
Its limitations must be known	Reportable range, Rate of no call, etc
Instrumentation must work optimally	Infrastructure qualification

In the case of LDTs



- *Clinical validity* of test:
 - Totally relies on analytical validity;
 - Cannot generalize easily (each lab has its own assay...)
 - Rarely replicated from published studies (\$\$\$);
- *Clinical utility (≠ perceived usefulness!)* :
 - Even less data ...
 - Frequently not documented even for FDA-approved tests ... Let alone LDTs ...



RESEARCH METHODS & REPORTING

STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies

 OPEN ACCESS

Incomplete reporting has been identified as a major source of avoidable waste in biomedical research. Essential information is often not provided in study reports, impeding the identification, critical appraisal, and replication of studies. To improve the quality of reporting of diagnostic accuracy studies, the Standards for Reporting Diagnostic Accuracy (STARD) statement was developed. Here we present STARD 2015, an updated list of 30 essential items that should be included in every report of a diagnostic accuracy study. This update incorporates recent evidence about sources of bias and variability in diagnostic accuracy and is intended to facilitate the use of STARD. As such, STARD 2015 may help to improve completeness and transparency in reporting of diagnostic accuracy studies.

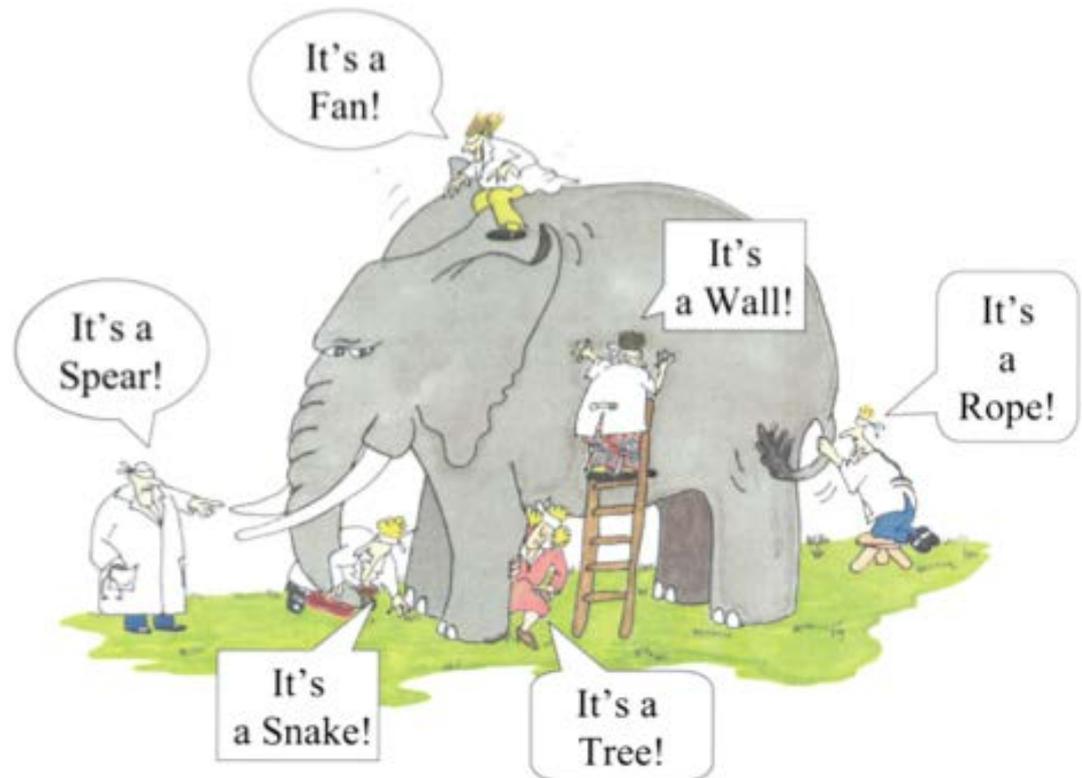
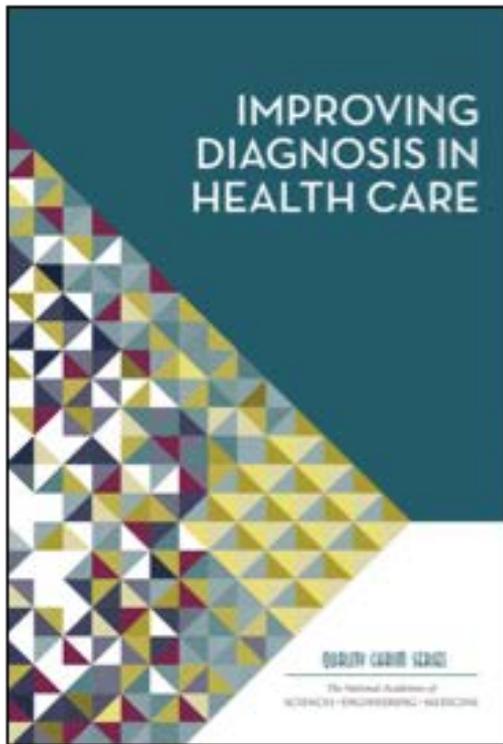
Patrick M Bossuyt¹, Johannes B Reitsma², David E Bruns³, Constantine A Gatsonis⁴, Paul P Glasziou⁵, Les Irwig⁶, Jeroen G Lijmer⁷, David Moher^{8,9}, Drummond Rennie^{10,11}, Henrica C W de Vet¹², Herbert Y Kressel^{13,14}, Nader Rifai^{15,16}, Robert M Golub^{17,18}, Douglas G Altman¹⁹, Lotty Hooft²⁰, Daniël A Korevaar¹, Jérémie F Cohen^{1,21}, for the STARD Group

Overinterpretation of Clinical Applicability in Molecular Diagnostic Research

Blanca Lumbreras,¹ Lucy A. Parker,^{1*} Miquel Porta,² Marina Pollán,³ John P.A. Ioannidis,⁴ and Ildefonso Hernández-Aguado¹

The requirements for the introduction of diagnostic tests into clinical practice are less strict than for the introduction of new treatments. Hence, flawed or exaggerated claims for diagnostic research results could lead to the premature adoption of defective tests, which could translate into erroneous decisions with adverse consequences for health. **All in all, our results emphasize the necessity for caution when interpreting the results of diagnostic accuracy studies in molecular research.**

Improving Diagnosis in Health Care



Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2015. *Improving diagnosis in health care*. Washington, DC: The National Academies Press.

The National Academies of
SCIENCE • ENGINEERING • MEDICINE

Challenges in (Laboratory) Medicine

- Limited resources for health care (unless you agree to pay more taxes)
- Rapidly increasing knowledge about disease and biology
- Increasing costs of certain treatments/interventions
- Continuous flow of health care innovations
- Rapidly changing technologies
- New health care paradigms (ex. « personalized medicine »)
- Very little research funding to validate Diagnostic Tests

Principles of Evidence-based Laboratory Medicine

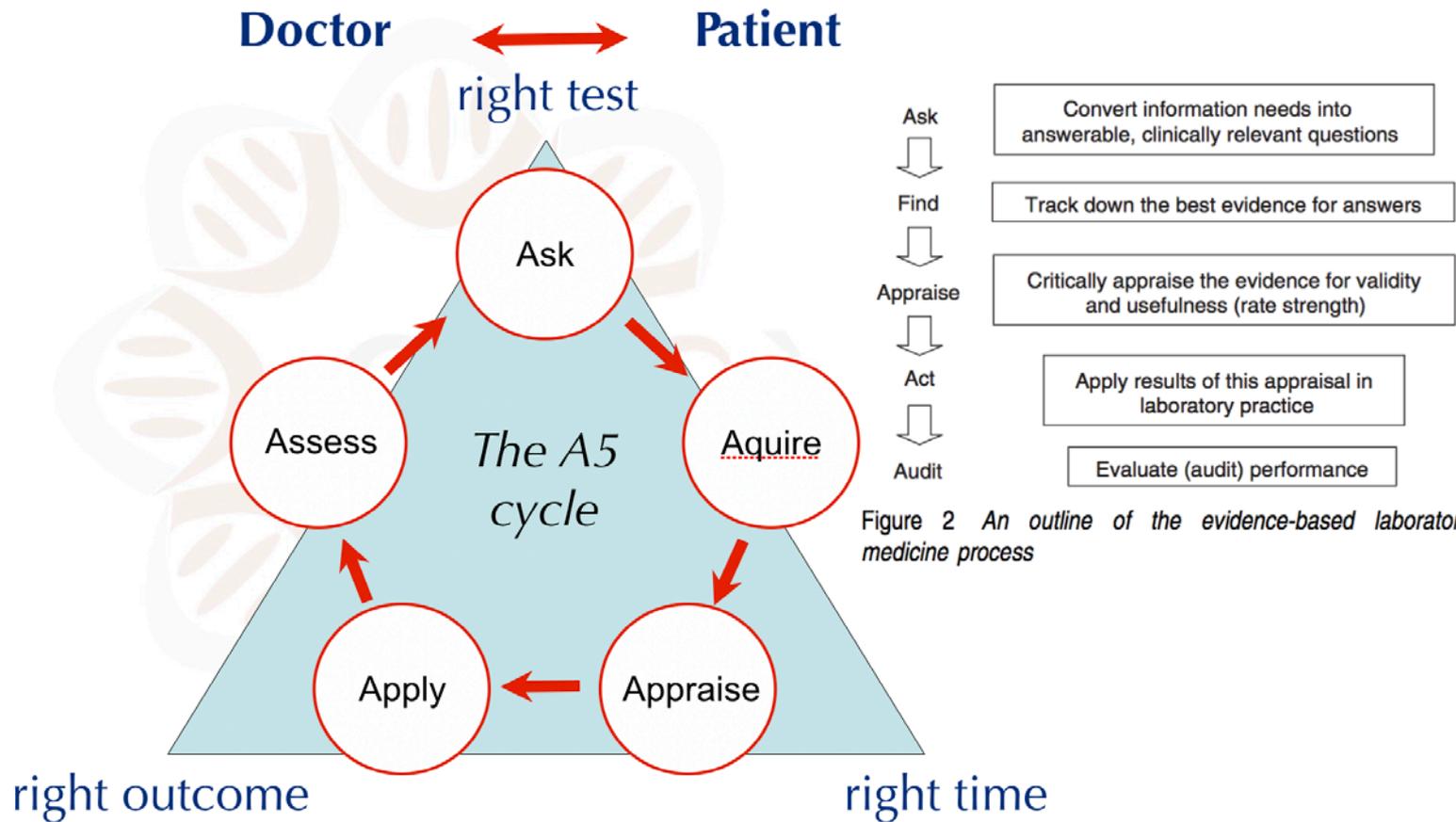


Figure 2 An outline of the evidence-based laboratory medicine process



Price et al. Applying evidence-based laboratory medicine. (2009) AACCPress

Merci !

Assessing the value of diagnostic innovation at Health Quality Ontario

Irfan Dhalla, MD, MSc, FRCPC

Vice-President, Evidence Development and Standards

Excellent Care for All Act 2010 laid the foundation for quality...



2ND SESSION, 39TH LEGISLATURE, ONTARIO
59 ELIZABETH II, 2010

2^e SESSION, 39^e LÉGISLATURE, ONTARIO
59 ELIZABETH II, 2010

Bill 46

*(Chapter 14
Statutes of Ontario, 2010)*

**An Act respecting
the care provided by
health care organizations**

Projet de loi 46

*(Chapitre 14
Lois de l'Ontario de 2010)*

**Loi relative aux soins
fournis par les organismes
de soins de santé**

.... and sets out HQO's mandate



Health Technology Assessment

- Evaluates:
 - Clinical benefit
 - Value for money
 - Patient preferences & equity issues
- Evaluation supports decisions about:
 - Public funding
- Also need guidelines/standards & quality improvement supports to get **right tests used in right patients at right time and interpreted in the right way**

Patient preferences & equity considerations

- Patient preferences
 - What issues are important to you?
 - What aspects of the test are important to you?
 - What is it like living with the health condition?
 - What are the barriers to accessing the test or treatment?
- Equity:
 - Are there unfair differences across patient characteristics (e.g., rural vs. urban)?

Ontario Health Technology Advisory Committee (OHTAC)

- A committee of the HQO Board of Directors
- Health care sector members, patients/public members, health economics, clinical epidemiology, ethics, industry, representation from variety of health care sectors
- OHTAC's recommendations are based on a careful review and deliberation of the health technology assessment, using an explicit framework for making decisions
- A genetics subcommittee will help OHTAC make recommendations about genetic tests

OHTAC Recommendation

- The Ontario Health Technology Advisory Committee recommends publicly funding [diagnostic test] in [patients with health condition who meet specific criteria]
- Rationale for recommendation explained and published
- Associated health technology assessment report also published

Diagnostic tests – last 2 years

- Cell cycle progression test for prostate cancer – **no**
- Long-term ECG monitoring - **yes**
- External loop recorders - **yes**
- MRI for breast cancer screening in non high risk – **no**
- Ultrasound for breast cancer screening in non high risk – **no**
- Skin testing for allergic rhinitis – **yes**
- Minimal residual disease in childhood leukemia – **yes**
- Transient elastography for liver fibrosis – **yes**
- Upright MRI – **no**
- Colon capsule endoscopy – **no**
- Pharmacogenetic test for depression – no recommendation

Two closing thoughts

- Health technology assessment should facilitate rapid uptake of diagnostic tests that help patients and provide reasonable value for money
- Health technology assessment methods and processes should be linked to guidelines, quality standards, quality improvement supports and performance monitoring so that the right test is used in the right patient in the right time and interpreted in the right way

Thank you

Assessing the value of diagnostic tests – the CADTH experience

Tammy J Clifford, PhD

CADTH Symposium

April 2017

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[@TammyJClifford](https://twitter.com/TammyJClifford)

CADTH Evidence
Driven.

Disclosures

- CADTH employee for 12 years
- Adjunct Professor, School of Epidemiology, University of Ottawa
- Nothing further to declare

What is HTA?

(Health) technology assessment ... is a multidisciplinary field of policy analysis. It studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology.

- From INAHTA (*International Network of Agencies for Health Technology Assessment*); www.inahta.org

What is HTA (2)?

- “...systematic evaluation of properties, effects, and/or impacts of health care technology. It addresses the direct, indirect, intended and unintended consequences ... Its main purpose is to inform technology-related policymaking in health care.”

- HTAi (www.htai.org)

CADTH

is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence about the optimal use of drugs and medical devices.

Our Programs and Services



DRUG REIMBURSEMENT RECOMMENDATIONS

- CADTH Common Drug Review (CDR)
- CADTH pan-Canadian Oncology Drug Review (pCODR)



HEALTH TECHNOLOGY MANAGEMENT PROGRAM

- Rapid Response Service
- Health Technology Assessment Service
- Optimal Use Service
- Environmental Scanning
- Horizon Scanning



OTHER PROGRAMS AND SERVICES

- Scientific Advice



KNOWLEDGE MOBILIZATION AND LIAISON OFFICERS

- Located in jurisdictions across Canada
- Understand the needs and priorities of local decision-makers
- Provide advice and tools to help turn evidence into policy and practice

CADTH's Proposed Process for the Assessment of Companion Diagnostics

1. Preamble

Companion diagnostics identify subgroups of patients for whom select drugs are likely to be most effective and safe. Based on feedback from participating jurisdictions, and guided by consultations with representatives internationally, across Canada, and among its committees, CADTH has developed a process for the assessment of companion diagnostics through the CADTH Common Drug Review (CDR) and pan-Canadian Oncology Drug Review (pCODR) programs.

2. Background

Companion diagnostics are laboratory tests that aim to measure the expression of a specific biomarker.¹ They guide optimal clinical management by identifying subpopulations of patients who are most likely to benefit from a given drug. These tests are distinct from other emerging molecular diagnostic techniques, such as whole genome sequencing, although most such technologies strive to tailor treatments to the needs of individual patients.

The global market for companion diagnostics is growing. The resulting implications for the Canadian health care system are significant, as there will be an increase in the number of drugs for which there are companion diagnostics. In 2013, the pCODR office reported that, on the horizon for cancer treatment, there were potentially 15 individual drugs and 31 drug-indication pairs linked to 12 different companion diagnostics.² Further, a 2015 survey conducted by CADTH found that 14% of new oncology submissions will have an associated companion diagnostic.³ Of note, these tests are not restricted to oncology drugs, and there are other conditions for which they have been developed, including cystic fibrosis, human immunodeficiency virus, rheumatoid arthritis, and hepatitis C.

The Canadian public reimbursement landscape for companion diagnostics is not well defined. Previous feedback from CADTH's stakeholders has included concerns regarding cross-jurisdictional inconsistency in the processes for approving, funding, and accessing these tests. Hence, there is an important need for pan-Canadian leadership in the development and implementation of a centralized process to inform public reimbursement decision-making for companion diagnostics.

https://www.cadth.ca/sites/default/files/pdf/CADTH_Consult_Proposed_Process_Companion_Diagnostics.pdf

CADTH Reports on Diagnostic Tests (past 2 years)

Health Technology Update (newsletter)

- Focus On: Direct-to-Consumer Genetic Testing (issue 18, in press)
- Self-Sampling for HPV and Other Sexually Transmitted Infections (issue 18, in press)
- [The Gastric Emptying Breath Test: A Tool to Assist the Diagnosis of Gastroparesis](#) (issue 17)

Issues in Emerging Health Technologies (bulletins)

- Point-of-Care Hemoglobin A1C Testing to Diagnose Type 2 Diabetes (in press)
- [Point-of-Care Testing for Influenza](#)
- [The Cytosponge: An Alternative to Endoscopy in Detecting Barrett Esophagus](#)
- [NephroCheck: A Bedside Biomarker Test to Identify Patients at Risk for Acute Kidney Injury](#)

Environmental Scans

- [Point-of-Care Testing: An Environmental Scan](#)
- [Pharmaceuticals Requiring Companion Diagnostics](#)
- [Cancer Biomarker Testing](#)

CADTH Reports on Diagnostic Tests (past 2 years)

Health Technology Assessment Reports

- [Comparative Value of Erythrocyte Sedimentation Rate \(ESR\) and C-Reactive Protein \(CRP\) Testing in Combination Versus Individually for the Diagnosis of Undifferentiated Patients with Suspected Inflammatory Disease or Serious Infection: A Systematic Review and Economic Analysis](#)

Optimal Use

- [HPV Testing for Primary Cervical Cancer Screening](#) (in progress)
- [Optimal Strategies for the Diagnosis of Acute Pulmonary Embolism](#) (in progress)
- [Mismatch Repair Deficiency Testing for Colorectal Cancer Patients](#)
- [Point-of-Care Troponin Testing in Patients with Symptoms Suggestive of Acute Coronary Syndrome](#)
- [Point-of-Care INR Testing Compared with Lab INR Testing: What Does the Evidence Say?](#)

CADTH Reports on Diagnostic Tests (past 2 years)

Pan-Canadian Oncology Drug Review

- 30/101 reviews (completed or ongoing as of March 31, 2017) have an associated companion diagnostic

Scientific Advice Program

- 2/6 submissions received to date have an associated companion diagnostic (1 oncology)

Rapid Response Program

- ~100 reports



Secretariat Support provided by:
CADTH
ACMTS

Meeting Summary
Health Technology Strategy Policy Forum Wider Table on Personalized Medicine

February 26th & 27th, 2015

Novotel Hotel, Toronto, ON

https://www.cadth.ca/sites/default/files/policy_forum_section/Wider_Table_Mtg_Summary_Feb_26-27_2015_Final_May_2015.pdf

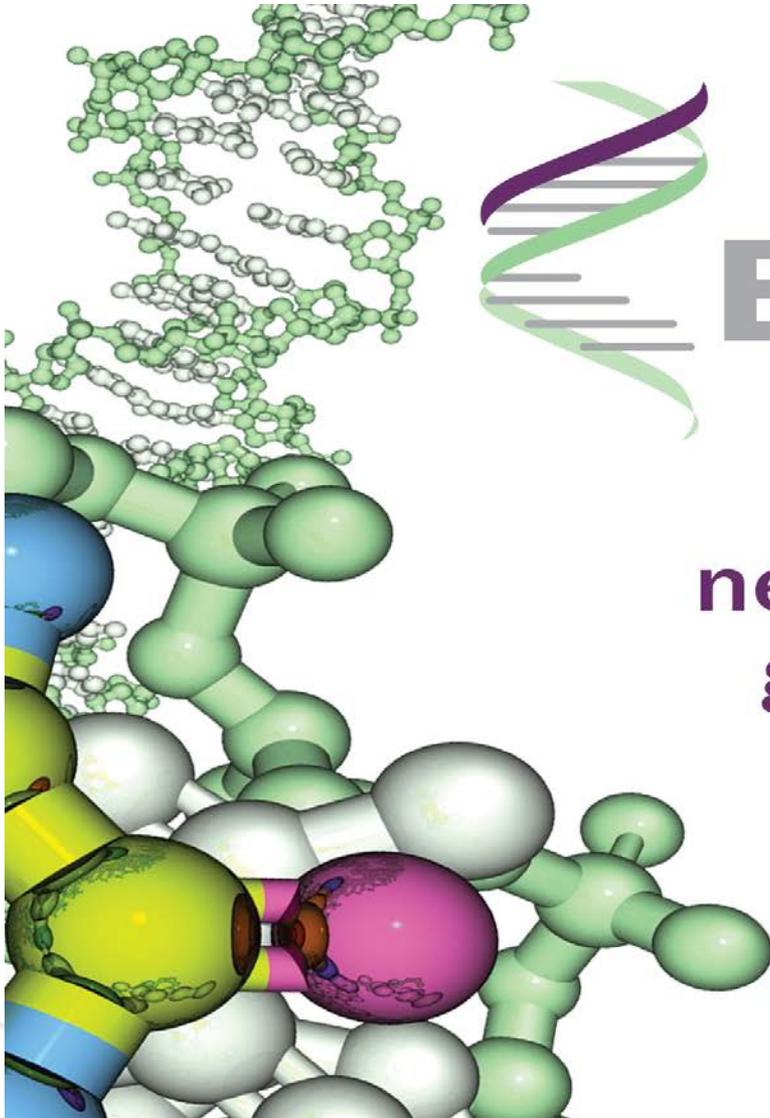
Policy Forum

Personalized Medicine – A Typology Briefing for CADTH

Stuart Hogarth, PhD¹

https://www.cadth.ca/sites/default/files/pdf/CADTH%20Personalized%20Medicine%20Typology%20Briefing_FINAL.pdf

Collaborations

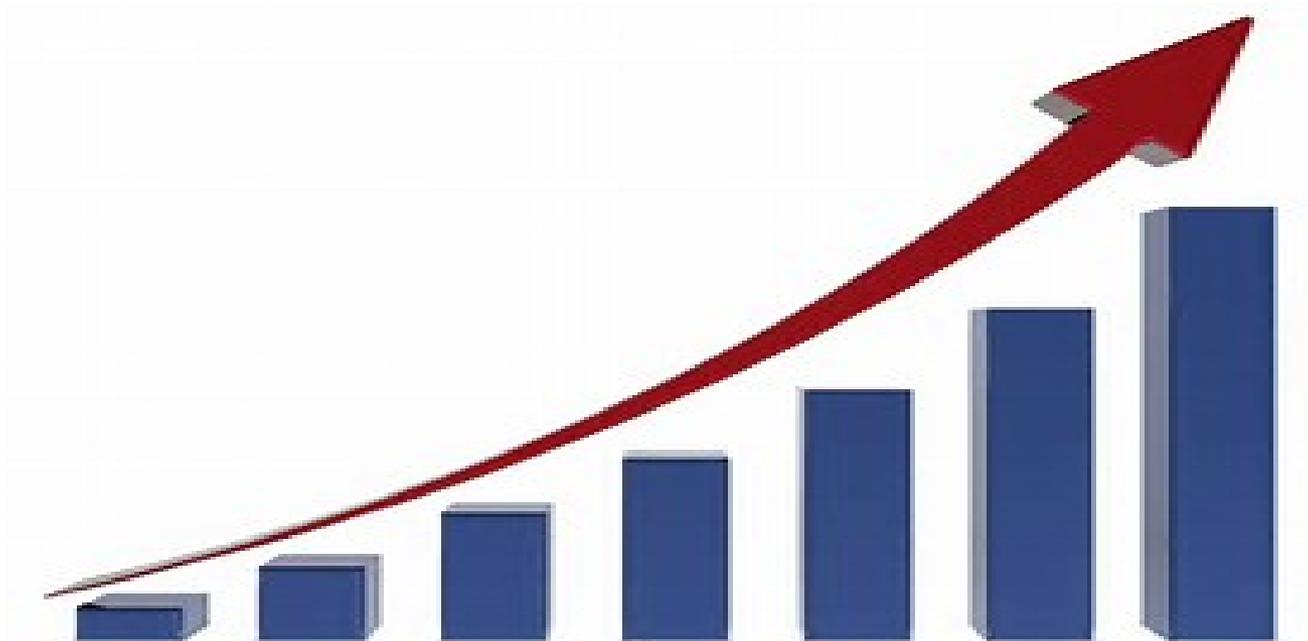


ECRIgene™

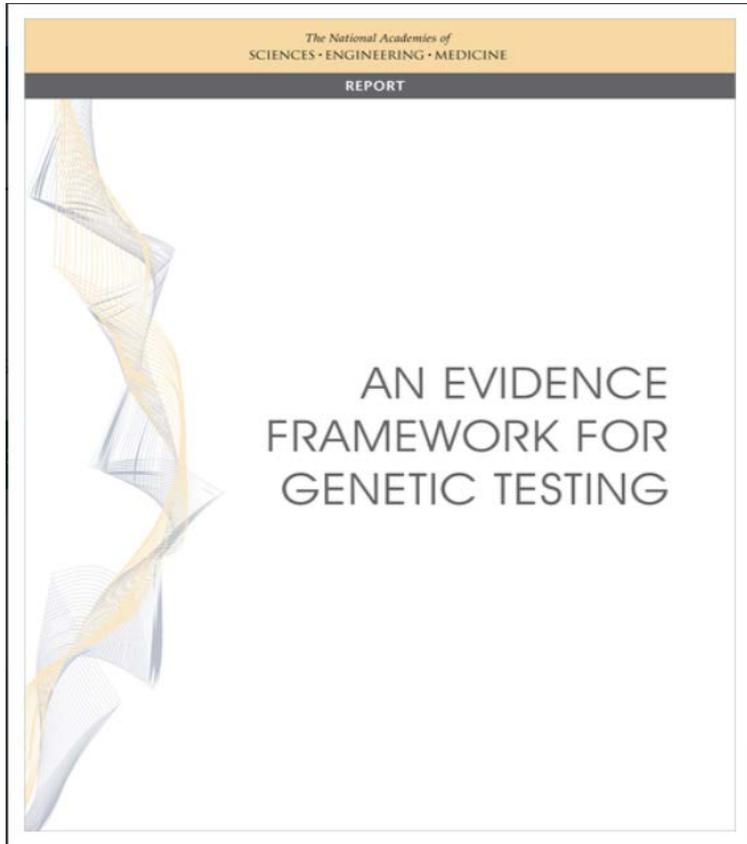
**A revolutionary
new resource on the
genetic tests that
matter most**

ECRIInstitute
The Discipline of Science. The Integrity of Independence.

Challenge #1 – Volume



Challenge #2 - Evidence



<https://www.nap.edu/catalog/24632/an-evidence-framework-for-genetic-testing>



Policy Perspective

Health Technology Assessment for Molecular Diagnostics: Practices, Challenges, and Recommendations from the Medical Devices and Diagnostics Special Interest Group



Susan Garfield, DrPH^{1,*}, Julie Polisena, MSc, PhD², Daryl S. Spinner, PhD, MBA³, Anne Postulka, MD⁴, Christine Y. Lu, MSc, PhD⁵, Simrandeep K. Tiwana, MBA, PhD^{6,7}, Eric Faulkner, MPH^{7,8,9}, Nick Poullos, PhD, PhM¹⁰, Vladimir Zah, PhD, BSc¹¹, Michael Longacre, BS¹²

[http://www.valueinhealthjournal.com/article/S1098-3015\(16\)00059-0/fulltext](http://www.valueinhealthjournal.com/article/S1098-3015(16)00059-0/fulltext)

Challenge #3 - Quality

February 17, 2015

FDA Regulation of Laboratory-Developed Diagnostic Tests

Protect the Public, Advance the Science

Joshua Sharfstein, MD¹

» [Author Affiliations](#) | [Article Information](#)

JAMA. 2015;313(7):667-668. doi:10.1001/jama.2014.18135

Conclusions

A patient travels by an ambulance that is regulated, to a hospital that is regulated, for care using medicines that are regulated, administered by nurses and physicians, who are regulated. Yet today, that same patient's life or death could hinge on whether a single, unregulated diagnostic test result is meaningful. The FDA is right to bring a measured approach to ensuring the quality, safety, and validity of laboratory-developed tests.

Challenge #4



Open

Making genomic medicine evidence-based and patient-centered: a structured review and landscape analysis of comparative effectiveness research

Kathryn A. Phillips, PhD¹, Patricia A. Deverka, MD, MS², Harold C. Sox, MD³,
Muin J. Khoury, MD, PhD⁴, Lewis G. Sandy, MD, FACP⁵, Geoffrey S. Ginsburg, MD, PhD⁶,
Sean R. Tunis, MD, MSc⁷, Lori A. Orlando, MD, MHS⁸ and Michael P. Douglas, MS⁹

Comparative effectiveness research (CER) in genomic medicine (GM) measures the clinical utility of using genomic information to guide clinical care in comparison to appropriate alternatives. We summarized findings of high-quality systematic reviews that compared the analytic and clinical validity and clinical utility of GM tests. We focused on clinical utility findings to summarize CER-derived evidence about GM and identify evidence gaps and future research needs. We abstracted key elements of study design, GM interventions, results, and study quality ratings from 21 systematic reviews published in 2010 through 2015. More than half ($N = 13$) of the reviews were of cancer-related tests. All reviews identified potentially important clinical applications

of the GM interventions, but most had significant methodological weaknesses that largely precluded any conclusions about clinical utility. Twelve reviews discussed the importance of patient-centered outcomes, although few described evidence about the impact of genomic medicine on these outcomes. In summary, we found a very limited body of evidence about the effect of using genomic tests on health outcomes and many evidence gaps for CER to address.

Genet Med advance online publication 13 April 2017

Key Words: comparative effectiveness research; genomic medicine; health policy; patient outcomes; systematic reviews

<http://www.nature.com/gim/journal/vaop/ncurrent/pdf/gim201721a.pdf>

CADTH Evidence
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ACMETS Preuves
à l'appui.