OLD TESTS, NEW TESTS, AND WHAT DO WE MAKE OF THEM?

Brian M. Gilfix
MDCM, PhD, FRCPC, DABCC, FAACC

March 26, 2019
Conflicts of Interest

• I have received honoraria from:
  – Alnylam Pharmaceuticals
  – Grifols, S.A.
  – Recordati Rare Diseases Canada
Objectives

1. To understand the role of the clinical laboratory in modern medicine
2. To understand why so few tests that appear in the literature make it into clinical usage.
3. To understand the process by which tests not available in Quebec can be ordered.
Questions

1. What percentage of tests that appear in the literature make it into clinical usage?

2. What is the difference between current troponin testing and high-sensitivity troponin?

3. Name one limitation in apoB testing?
Importance of This Year 2019

International Year of the Periodic Table of Chemical Elements (150 years)
Dimitry Mendeleev

The Periodic Table
by Primo Levi
(100th anniversary of his birth)
McGill University Clinical Laboratories

- Located on the 4th and 5th floors of Pavilion E at the Glen site
- Part of OPTILAB cluster (‘grappe”)
- MUHC
  - 5.3 million billable tests annually
  - 5,000- 6000 specimens per day
Most complex “Grappe”

- One laboratory on multiple sites
- $99M
- 850 Employees
- 120 MDs

- Grappe Leadership accountable to PDG of MUHC (fiduciary)
- Academic strengths

Source: A. Dascal
Use of Diagnostic Tests in the Patient Pathway

Screening → Risk Stratification → Diagnosis → Treatment Selection → Monitoring

One Test = One Result = One Action
What we wish to avoid?

Please send a copy to:

☐ Lachine Campus
McGill University Health Centre
Division of Cardiology
650, 16th Avenue
Lachine, Quebec
H9S 3NS
Phone: (514) 637-2351
ext: 77250
Fax: (514) 637-0951

☐ Centre Medical Notre-Dame Lachine
1515 Notre-Dame Street
Lachine, Quebec
H8S 2E4
Phone: (514) 634-7146
Fax: (514) 634-7147

Laboratory Tests

☐ Copy to: ___________________________  Lachine Dossier: ___________________________
Date Requested: ___________________________  Date of test: ___________________________

☒ Electrolytes & Renal Profile
  • Na / K / Cl / HCO3 / Ca / Mg / PO4 / Urea / Creatinine

☒ Liver Profile
  • AST / ALT / Alk Phos / GGT / T. Bilir / CK / LDH

☒ Lipid Profile
  • Total Cholesterol / HDL-C / LDL-C / TG / TC-HDL Ratio
  • Apolipoprotein A / Apolipoprotein B

☒ Metabolic Profile
  • Fasting Glucose / HbA1c / TSH / Free T4 / Free T3

☒ Coagulation Profile
  • PT / INR / PTT

☒ Hematology Profile
  • Hemoglobin / White Blood Cell Count / Platelets / Differential

☒ Hypercoagulability Workup
  • Protein C, Protein S, APC, Prothrombin Gene, Factor V Leiden
  • Anti-Phospholipid Anti-Body, Homocystein

☒ Anemia Profile
  • Folate / Vitamin B12 / Smear / Iron Studies / Ferritin

☒ Other: ___________________________

MD
In a hospital chart, what percentage of the objective information is generated by the hospital laboratory?

1. 80%
2. 70%
3. 50%
4. 30%
5. 10%
In a hospital chart, what percentage of the objective information is generated by the hospital laboratory?

1. 80%
2. 70%
3. 50%
4. 30%
5. 10%

Is it possible to know or be familiar with every test?

☐ Yes
☐ No
No!

- The Mayo Interpretive Test Catalogue is over 700 pages long.
- In 50 years, the number of tests has grown from ~250 to > 4000
- New tests are appearing faster than old tests are disappearing, especially for MolDx (one of the fastest growing segments).
Problematic Tests

Obsolete Tests
- CK-MB
- Schilling test
- FTI
- Prostatic acid phosphatase
- Bence-Jones protein
- LE cell test
- Fecal leukocytes
- RBC folate
- Porphyrin screening tests

(Very) Limited Utility
- ESR
- Serum folate
- Myoglobin
- APCR ratio
- AST
- MTHFR 677C>T
Progress in Medicine = Progression of Analytical Tools
An Example from Oncology

<table>
<thead>
<tr>
<th>Year</th>
<th>Landmarks in the application of analytical tools to inform cancer diagnosis, prognosis, and therapy</th>
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</thead>
<tbody>
<tr>
<td>1847</td>
<td>Microscopy</td>
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<tr>
<td></td>
<td>Formal description of leukemia by Rudolf Virchow\textsuperscript{190,191}</td>
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<tr>
<td>1941</td>
<td>Cytopathology</td>
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<td></td>
<td>Hematoxylin and Eosin (H&amp;E) staining of Papanicolaou-smear, cervical cancer\textsuperscript{192,193}</td>
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<tr>
<td>1956</td>
<td>Improved karyotyping: accurate determination of human chromosome numbers\textsuperscript{194,195}</td>
</tr>
<tr>
<td>1960s</td>
<td>Cytogenetics</td>
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<tr>
<td></td>
<td>Philadelphia chromosome, chronic myeloid leukemia (CML)\textsuperscript{196}</td>
</tr>
<tr>
<td></td>
<td>Electron microscopy</td>
</tr>
<tr>
<td></td>
<td>Epstein–Barr Virus (EBV) associated with Burkitt’s lymphoma\textsuperscript{197}</td>
</tr>
<tr>
<td>1970s</td>
<td>Chromosome banding</td>
</tr>
<tr>
<td></td>
<td>Recurrent translocations in hematological malignancies\textsuperscript{198–204}</td>
</tr>
<tr>
<td></td>
<td>Radioimmunoassay</td>
</tr>
<tr>
<td></td>
<td>Carcinoembryogenic antigen (CEA), colorectal cancer\textsuperscript{205,206}</td>
</tr>
<tr>
<td></td>
<td>DNA sequencing</td>
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<tr>
<td></td>
<td>\textsuperscript{207–208}, molecular cloning\textsuperscript{210}</td>
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<tr>
<td>1980s</td>
<td>Chromosome banding</td>
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<tr>
<td></td>
<td>Recurrent translocations in sarcomas/soft tissue tumors\textsuperscript{211–214}</td>
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<tr>
<td></td>
<td>Radioactive probe hybridizations</td>
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<td>Detection of BCR-ABL1, CML\textsuperscript{215}, IgH-BCL2, B-cell lymphoma\textsuperscript{216}, TcR-MYC, T-cell leukemia\textsuperscript{217}, human papilloma virus (HPV) in cervical cancer\textsuperscript{218}</td>
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<td>Fluorescence \textit{in situ} hybridization (FISH)\textsuperscript{219, 220}</td>
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<td>ERBB2 in breast cancer\textsuperscript{221}</td>
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<td></td>
<td>Flow cytometry</td>
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<td>Acute promyelocytic leukemia (APML)\textsuperscript{222}, neuroblastoma\textsuperscript{223}, myelodysplastic syndrome (MDS)\textsuperscript{224}, multiple myeloma\textsuperscript{225}</td>
</tr>
</tbody>
</table>

**Oncogenes and tumor suppressors: identification and characterization, e.g., RAS, MYC, RB\textsuperscript{1,226–228}**

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<td>Radioimmunoassay</td>
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<tr>
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<td>Estrogen receptor\textsuperscript{228}, prostate specific antigen\textsuperscript{230}</td>
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<tr>
<td></td>
<td>Immunohistochemistry</td>
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<td></td>
<td>Estrogen receptor\textsuperscript{228, 231}, ERBB2\textsuperscript{232, 233}</td>
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<tr>
<td></td>
<td><strong>Invention of PCR\textsuperscript{234}</strong></td>
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<tr>
<td></td>
<td>Reverse transcriptase PCR (RT-PCR)</td>
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<tr>
<td></td>
<td>BCR-ABL1 in CML, PML-RARA in APML\textsuperscript{236}, AML1/ETO in AML (acute myeloid leukemia)\textsuperscript{237}</td>
</tr>
</tbody>
</table>

**Human Genome Project\textsuperscript{238, 239}**

<table>
<thead>
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<th>Year</th>
<th>Landmarks in the application of analytical tools to inform cancer diagnosis, prognosis, and therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990s</td>
<td>Microarray profiling for high-throughput genomic and transcriptomic profiling of cancers\textsuperscript{243}</td>
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<tr>
<td></td>
<td>Expression profiles of cancers\textsuperscript{244, 245} diffuse large B-cell lymphoma (DLBCL) subtypes\textsuperscript{246}, breast cancer prognosis\textsuperscript{247}, hereditary breast cancer\textsuperscript{248}, biomaekers of prostate cancer\textsuperscript{249}, lung cancer\textsuperscript{250}, gene fusions in prostate cancer\textsuperscript{251}</td>
</tr>
<tr>
<td>2000s</td>
<td>PCR amplification and sequencing of “cancer genes”\textsuperscript{252} from tumor specimens</td>
</tr>
<tr>
<td></td>
<td>Genomic landscapes of somatic aberrations in different cancers-breast, colorectal, pancreatic\textsuperscript{253–256}</td>
</tr>
<tr>
<td></td>
<td>Massively parallel high-throughput/next-generation sequencing\textsuperscript{257–259}</td>
</tr>
<tr>
<td></td>
<td><strong>TCGA - The Cancer Genome Atlas\textsuperscript{260–264}, <a href="https://cancergenome.nih.gov/">https://cancergenome.nih.gov/</a></strong></td>
</tr>
</tbody>
</table>

Various modalities of precision oncology projects in research, clinical, and clinical trial settings discussed in this review

**Precision Medicine Initiative\textsuperscript{265, 266}**

BUT!
Gartner’s Hype Cycle

- Peak of Inflated Expectations (Hype)
- Technology Trigger
- Trough of Disillusionment
- Plateau of Productivity
Trend in the Number of Biomarkers-related NIH-funded Grants and Publications

Fig. 1. Trend in the number of biomarker-related NIH-funded grants and related publications over 2½ decades.

FDA-cleared Protein Tests
Introduced 1993-2013

Association between biomarkers and disease often overstated

• Analysis of 35 of the most highly cited studies published between 1991 and 2006 in 10 well-regarded biomedical journals
• Each of the studies had been referenced by at least 400 subsequent papers; some had citations numbering in the thousands.
• The studies analyzed the relationships between biomarkers such as the presence of specific genes or infections, levels of blood proteins and other markers with the likelihood of developing conditions such as cancer and heart disease.
• For 29 of 35 studies included in their analysis, the subsequently published meta-analysis reported a less optimistic effect size estimate than the highly cited study.

Ioannidis JPA, Pangioyou OA. JAMA 2011;305:2200-10.
Figure. Relative Risks in the Highly Cited Studies vs the Corresponding Largest Studies and in the Highly Cited Studies vs the Corresponding Meta-analyses

Diagonal lines represent equal effects between the highly cited study and the largest study (A) or the meta-analysis (B), respectively. A, Not shown are 3 topics whereby the highly cited study was the same as the largest study. B, Meta-analyses may include the data from the highly cited studies, but the latter are usually small compared with the corresponding meta-analyses (median, 5%; interquartile range, 2%-12%, of the meta-analysis sample size).

Ioannidis JPA, Pangioyou OA. JAMA 2011;305:2200-10.
Diagnostic Biomarkers: Are We (actually) Moving from Discovery to Clinical Application?

- Number of previously reviewed studies published in 2006 that evaluated the diagnostic value of a molecular or -omics based test: 107
- Number of articles reviewed citing these studies over 10 year period 2006-2016: 4259
- Number of studies continuing research on the diagnostic value of the molecular or –omics-based test: 118
- Number of studies reporting progress in validation of the test for use in clinical practice (or 21% waste): 93

How do you define progress?

BOX 1.
Types of progress in validation of molecular- or “-omics”-based diagnostic tests for use in clinical practice.

- Advance in the clinical validation: Further study reporting the diagnostic accuracy of the test in an independent patient series comparable to the population on whom the test would be used in practice.

- Technical improvement: Further study reporting modification of the assay or computational procedures to improve diagnostic accuracy.

- Extended diagnostic application: Further study reporting application of the test to a different diagnostic question in the same disease, independently of the study design used.

- Economic evaluation*: Further study performed specifically to estimate the cost of using the test in clinical practice.

- Clinical use or implementation*: Further study evaluating the effect of using the test in practice or addressing questions relevant to implementation of the test in practice (e.g., resources needed, training, turnover time).

*Only applicable if the clinical validity has previously been established in an independent patient series comparable to the population on whom the test would be used in practice.
Progress in the validation of 107 molecular diagnostic tests for use in clinical practice over a 10-year period

107 molecular tests published

33 PCR based tests subjected to continued diagnostic research
28 made progress toward clinical application
17 clinical validation
13 technical advance

44 proteomic based tests
4 made progress in toward clinical application

Limitation on the Acceptance of a Test: Cholesterol versus ApoB-100

• Cholesterol
  – CDC reference method (Abell-Levy-Kendall-Brodie-Kendall method + IDMS) for total cholesterol is considered the “gold standard” for cholesterol measurement.
  – It served as the accuracy base for all of the epidemiologic studies and clinical trials on which the relation of increased blood cholesterol to CHD is based and the medical decision points were derived.
  – Since 1988, there has been a program for standardization and traceability of cholesterol measurements to the National Reference System for Cholesterol (NRS/CHOL)

• OUTCOME: Improved test reliability

Limitation on the Acceptance of a Test: Cholesterol versus ApoB-100

• ApoB100
  – Calibration standards: CLSI-C37A native protein with assigned value (secondary reference material)
  – apoB is found in other particles: VLDL, IDL, Lp(a), Chylomicron remnants
  – Lacks traceability and standardization to a Système international unit (i.e. moles)
  – Current objective of a IFCC working group is a peptide based calibration MS-based (traceable)

Precision and accuracy of 10 methods for non-HDL-P determination

Delatour er al. Clin Chem 2018;
Errors In Databases?

- HGMD
  - Of 239 unique variants described as disease causing only 7.5% fit this category

- OMIM/HGMD
  - 27% of annotations for recessive disease-causing variants are incorrect

- ClinVar/ClinGen
  - Only 56,742/172,870 had at least one-star entry
  - variants are classified into at least three clinical-significance tiers, and the methods used for the assignment and supporting evidence must be provided.

- Consequence on mutation assessment?

Nature Methods 2016;13:103
Liquid Biopsies: The Promise

• What it is? Analysis of cell-free circulating tumor (ct)DNA in blood

• The Prize
  – Identify metastatic disease early on
  – Non-invasively
  – Cost-effectively

Patients negative for cell-free DNA (cfDNA) alterations in both tests were classified as complete congruence for 0 alterations (9/40 [22.5%]). For congruence analysis, patients who had 1 or more alterations reported, but none was covered by both tests, were excluded and classified as not evaluable for patient-level congruence (6/40 [15%]). The proportion of patients with complete congruence for 1 or more alterations, partial, and no congruence was 3 of 40 (7.5%), 6 of 40 (15%), and 16 of 40 (40%), respectively, among the 2 platforms.

- Blood samples from 40 patients with prostate cancer sent to two different clinical laboratories: Guardant360 & Personal Genome Diagnostics
- 65% of specimens had only partial or no congruence
Planned Introduction of Beckman hsTnI on March 28, 2019 at noon at all MUHC sites
Beckman hsTnI

• Higher Analytical precision at lower concentrations - Improves low-end measuring range with a demonstrated limit of detection (LoD) at 2.3 ng/L
  – Enables precise and reliable measurement of low troponin levels
• Greater clinical sensitivity for myocardial injury - Meets all high sensitivity requirements defined by international guidelines
  – Measures cardiac troponin (cTn) values above the LoD in >50% of a healthy population
  – Demonstrates optimal precision: <10% CV imprecision at the 99th percentile upper reference limit (URL)
• Demonstrates excellent correlation and concordance with the current AccuTnI+3 assay (NOT IDENTICAL)
• Accurate recognition of small changes - Provides delta values and sex-specific 99th percentile URL values
• Reduces analytical false positives
• cTnI biology remains the same!
hsTnI: Some Key Points

• The ideal test has high both sensitivity and NPV.
• An elevated hs-cTn identifies the presence of myocardial injury but not the mechanism or underlying cause.
• Myocardial injury outside that occurring in the setting of AMI can create diagnostic challenges but should not be discarded as a nuisance abnormality, because it is associated with a poor cardiovascular prognosis.
• Terms such as “troponin leak,” “troponinemia,” or “troponinitis” are unadvisable because such terms trivialize the prognostic meaning of myocardial injury.

Januzzi et al. JACC 2019;73:1059
hsTnI: More Key Points

• The absolute change in Tn has greater diagnostic accuracy for AMI than relative change criteria.

• A cutoff set at or near the LoD of the hs-cTnI assay achieves very high NPV for AMI.
The Hope: A Clear Algorithm allowing Rapid Patient Disposition in the ER and Only in the ER

Figure 1: 0 hour/3 hour rule-in/rule-out algorithm for non-ST elevation acute coronary syndromes from ESC guidelines

Acute Chest Pain

hs-cTn < URL

- Pain > 6 hours
  - Re-test hs-cTn: 3 hours
    - hs-cTn no change
      - Pain-free, GRACE < 140, differential diagnoses excluded
        - Discharge/stress testing
    - ∆ change* (l value > URL)
      - GRACE = Global Registry of Acute Coronary Events score
      - hs-cTn = high sensitivity cardiac troponin
      - URL = upper reference limit, 99th percentile of healthy population
      - * ∆ change dependent on assay. Highly abnormal hsTn defines values beyond 5-fold the URL.

hs-cTn > URL

- Pain < 6 hours
  - Invasive management
- hs-cTn no change
  - Highly abnormal hs-cTn + Clinical presentation

Contact information
For more information about the Access hsTnI assay or for reagent ordering you can:
- Visit the Beckman Coulter website: http://www.beckmancoulter.com
- Contact your local Beckman Coulter representative
Planned Guidance

MYOCARDIAL DAMAGE/INFARCTION IS RULED OUT IN PATIENTS:
  presenting with chest pain greater than 3 hours since onset without
  clinical evidence of ischemia and hsTnI less than or equal to 6 ng/L in
  initial sample
  (LoD = 2.3 ng/L)

OR:
  hsTnI less than or equal to 17.5 ng/L in initial sample and delta(change)
  less than or equal to 5 ng/L, 3 hours later.
  (PPV=66% & NPV=97%)

CONSIDER MYOCARDIAL DAMAGE/INFARCTION IF:
  hsTnI is greater than or equal to 87.5 ng/L in initial sample OR delta (change)
  greater than or equal to 22 ng/L 3 hours later, with clinical evidence of
  ischemia.
  (PPV=90% & NPV=94%)
But, will we be seeing a lot more positives?

<table>
<thead>
<tr>
<th>Access hsTnI</th>
<th>+ve &gt;17.5 ng/L</th>
<th>-ve ≤17.5 ng/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accu TnI+3</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>+ve &gt;0.04 µg/L</td>
<td>6</td>
<td>31</td>
</tr>
</tbody>
</table>

Accuracy = 54/60 x 100% = 90% (79-96% CI)

B. Gilfix. In house evaluation study - Lachine
WHAT ABOUT TESTS THAT ARE NOT DONE IN-HOUSE?
Send-Out Tests?

• On the island of Montreal
  – As on April 1, 2010, these are no charge.

• In the Province of Quebec
  – Usually does not require approval by a Laboratory Physician (Medical Biochemistry, Hematology, Microbiology, Medical Genetics)
Send-Out Tests?

- Outside of the Province of Quebec
  - Always requires approval by a Laboratory Physician (Medical Biochemistry, Hematology, Microbiology, Medical Genetics)
  - RAMQ AH-612 form signed by requesting physician AND Laboratory Physician and sent before sample is drawn
  - Why?
    - Is test justified?
    - What is the sample type?
    - How is it handled & stored?
    - Where is test done?
AUTORISATION POUR DES SERVICES DE BIOLOGIE MÉDICALE NON DISPONIBLES AU QUÉBEC

À REMPLIR PAR LE PROFESSIONNEL AUTORISÉ À PRESCRIRE

<table>
<thead>
<tr>
<th>Identité de l’usager</th>
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<tbody>
<tr>
<td>Prénom</td>
<td>Date de naissance</td>
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<tr>
<td>Annee</td>
<td>Mois</td>
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<td>Numéro d’assurance maladie</td>
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<td>Numéro de dossier</td>
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<table>
<thead>
<tr>
<th>Identité du professionnel autorisé à prescrire</th>
<th></th>
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<tbody>
<tr>
<td>Prénom</td>
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<td>Ind. r. N° de télécopieur</td>
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<td>Nom de l’établissement</td>
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| Diagnostic et services demandés               |  |
| Diagnostic                                   | Code OMIM ou autre |
| Génotese en cours                            | Oui              |
| Non                                          |  |
| Services de biologie médicale demandés       |  |

| Renseignements complémentaires concernant les services demandés |  |
| Si analyse génétique pour maladie héréditaire : confirmation d’absence de mutation familiale connue |  |
| Renseignements complémentaires concernant les services demandés |  |
| Si pertinent, joindre des documents supplémentaires (ex. : arbre généalogique) |  |

<p>| Signature du professionnel autorisé à prescrire |  |
| Prénom                                        | Date de | Année | Mois | Jour |
| Prénom                                        | Date   | Année | Mois | Jour |</p>
<table>
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**A REMPLIR PAR LE MÉDECIN APPROBATEUR**

Identité du médecin approbateur rattaché à un établissement désigné
(médecin généticien ou médecin de laboratoire ayant une compétence officiellement reconnue par son établissement dans le domaine concerné par la demande d’analyse)

<table>
<thead>
<tr>
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Établissement désigné :

- [ ] CHU Sainte-Justine
- [ ] CHUS
- [ ] CHUM
- [ ] CHUQ
- [ ] CUSM
- [ ] HMR
- [ ] HGJ
- [ ] CHAUQ

Adresse

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</table>

La demande est :

- [ ] autorisée
- [ ] annulée après discussion avec le professionnel prescripteur

Établissement où les services de biologie médicale seront réalisés

<table>
<thead>
<tr>
<th>Nom de l’hôpital ou du laboratoire</th>
<th>Nom et prénom du médecin responsable</th>
<th>Coût estimé des services ($ CAD)</th>
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Adresse

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<tr>
<th>Numéro</th>
<th>Rue</th>
<th>Bureau</th>
<th>Ville</th>
<th>Province/État</th>
<th>Pays</th>
<th>Code postal</th>
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J’atteste que, autant que je sache, les services de biologie médicale sont :

- [ ] cliniquement requis;
- [ ] non disponibles au Québec;
- [ ] non disponibles au Canada (dans le cas d’une demande de services à l’extérieur du Canada).

Signature du médecin approbateur

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<tr>
<th>Date</th>
<th>Année</th>
<th>Mois</th>
<th>Jour</th>
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Coût réel des services ($ CAD)

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Signature du directeur des ressources financières de l’établissement désigné

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<th>Mois</th>
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Examples of Commonly Used Outside Laboratories

• Criteria:
  – Must be clinically certified laboratory
  – Not research laboratory
  – Canada 1st

• Examples:
  – In Common Laboratories (Ontario)
  – Mayo Medical Laboratories
  – ARUP Laboratories
  – Quest Laboratories
  – Athena Laboratories
  – Prevention Genetics
  – GeneDx
Process for Obtaining of Approval for Out-of-province testing at MUHC

AH-612 Form Received at Send-out bench

Sent for approval

Approved

Not Approved

Decision

Typical reasons for not being approved:
• test available in Quebec
• test not available in a clinical lab
• test not validated (e.g. available in a single commercial lab & all literature comes from that lab)
• too broad or expensive in clinical context (e.g. Is it AR, AD, or X-linked? Is testing for a common cause more efficient than testing for a rare cause?)

Reason written on 2nd page by approver. Initialed and dated.

Form stamped "Not approved".

Signed form faxed back to MD requesting to have sample drawn

Signed form faxed back to Laboratory (non-MUHC)

Signed form filed. Request entered into database.

MUHC samples

Yes

No

Samples sorted, logged in and stored in fridge/freezer. RAMQ dataset is updated and sample(s) are sent to external laboratory.

RAMQ AH-612 is registered in RAMQ dataset. RAMQ request is valid for 1-year

Fax approved/refused RAMQ AH-612 back to requesting physician

BMG
What to Expect in the Next 12 Months?

• Revised lymphocyte stimulation test (final stage)
• NT-ProBNP
• Alzheimer disease
• Vitamin B12 metabolism
• Alpha1-Antitrypsin