Precision Medicine and the General Internist

Finlay A. McAlister, MD FRCPC
Division of General Internal Medicine
University of Alberta
The following presentation represents the views of the speaker at the time of the presentation. This information is meant for educational purposes, and should not replace other sources of information or your medical judgment.

**Conflict Disclosures**

I have no conflicts to declare.
Sumit (Me2) Majumdar (1966-2018)
Precision Medicine and the General Internist

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“If it were not for the great variability among individuals, medicine might as well be a science, not an art”
Learning Objectives

1. To describe precision medicine

2. To review the current status of precision medicine efforts relevant to General Internal Medicine practice

3. To explore the potential benefits, and limits, of precision medicine in the practice of General Internal Medicine
What do I know about precision medicine?

• I spent 3 summers doing genetics research and worked in a human genetics lab in Edinburgh in 1988
But that was a long long time ago
What is Precision Medicine?

McAlister et al. CMAJ 2017;189:E1065-E1068
The rationale for precision medicine

1) Even efficacious Rx’s benefit only a small minority of pts
   – Yet all are exposed to risks and costs
FACT SHEET: President Obama’s Precision Medicine Initiative

Building on President Obama’s announcement in his State of the Union Address, today the Administration is unveiling details about the Precision Medicine Initiative, a bold new research effort to revolutionize how we improve health and treat disease. Launched with a $215 million investment in the President’s 2016 Budget, the Precision Medicine Initiative will pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients.

Most medical treatments have been designed for the “average patient.” As a result of this “one-size-fits-all-approach,” treatments can be very successful for some patients but not for others. This is changing with the emergence of precision medicine, an innovative approach to disease prevention and treatment that takes into account individual differences in people’s genes, environments, and lifestyles. Precision medicine gives clinicians tools to better understand the complex mechanisms underlying a patient’s health, disease, or condition, and to better predict which treatments will be most effective.
BMJ: Clinical Evidence

- 1/3 of what we do is effective (or likely to be effective);
- 50% unknown;
- and 15% harmful or unlikely to be effective

Effectiveness of 3000 treatments as reported in randomised controlled trials selected by Clinical Evidence. This does not indicate how oftentreatments are used in healthcare settings or their effectiveness in individual patients.
IMPRECISION MEDICINE

For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

1. ABILIFY (aripiprazole)
   Schizophrenia

2. NEXIUM (esomeprazole)
   Heartburn

3. HUMIRA (adalimumab)
   Arthritis

4. CRESTOR (rosuvastatin)
   High cholesterol

5. CYMBALTA (duloxetine)
   Depression

6. Advair Diskus (fluticasone propionate)
   Asthma

7. ENBREL (etanercept)
   Psoriasis

8. REMICADE (infliximab)
   Crohn's disease

9. COPAXONE (glatiramer acetate)
   Multiple sclerosis

10. NEULASTA (pegfilgrastim)
    Neutropenia

Based on published number needed to treat (NNT) figures. For a full list of references, see Supplementary Information at go.nature.com/4dr78f.
Outcomes from a Study

= Good Outcome

= Intermediate Outcome

= Bad Outcome

Mean Treatment Difference

Risk Stratification
MADIT-II
(death 14.2% vs. 19.8%, OR 0.69, 95% CI 0.51-0.93)

31% reduction in risk of all-cause mortality

M. Felker et al, Duke
MADIT-II: 80% Survive Regardless of Intervention

- Do not benefit from intervention (14.2%)
- Benefit (5.6%)
- Survive regardless of the intervention (80%)
Delivering Precision Medicine

Outcomes from a Study

Risk Stratification

Genetics
Pharmacogenomics

Clinical Risk-Stratification

Proteomics
Biomarkers

<table>
<thead>
<tr>
<th>GRACE™ ACS Risk Model 0.36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>40-49</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probability of in-hospital Death or MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
</tr>
<tr>
<td>11%</td>
</tr>
<tr>
<td>15%</td>
</tr>
</tbody>
</table>

To 6 months
The rationale for precision medicine

1) Even efficacious Rx’s benefit only a small minority of pts
   – Yet all are exposed to risks and costs

2) Large RCTs of similar phenotype pts needed to show small-modest benefits
   – Subgroups defined by single variables
   – Then we extrapolate to older, sicker pts with multiple comorbidities and meds
Trial participants

Clinical practice
Comorbidity burdens are high, and increasing. 65% of Medicare beneficiaries have 2 or more chronic conditions.

Table 3. Prevalence, Annual Costs, and Comorbidity by Major Diagnostic Category (MDC)*

<table>
<thead>
<tr>
<th>MDC</th>
<th>% With ≥4 Conditions</th>
<th>Mean Expenditures for All Patients, $</th>
<th>Prevalence of Type of Condition, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloproliferative</td>
<td>80</td>
<td>19,839</td>
<td>2</td>
</tr>
<tr>
<td>Kidney</td>
<td>74</td>
<td>18,896</td>
<td>6</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>72</td>
<td>17,123</td>
<td>1</td>
</tr>
<tr>
<td>Blood and immunological</td>
<td>67</td>
<td>13,366</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system</td>
<td>66</td>
<td>13,516</td>
<td>12</td>
</tr>
<tr>
<td>Digestive</td>
<td>63</td>
<td>13,093</td>
<td>4</td>
</tr>
<tr>
<td>Mental</td>
<td>62</td>
<td>12,537</td>
<td>13</td>
</tr>
<tr>
<td>Ear, nose, throat</td>
<td>62</td>
<td>9,686</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory</td>
<td>60</td>
<td>14,303</td>
<td>15</td>
</tr>
<tr>
<td>Female reproductive</td>
<td>59</td>
<td>10,364</td>
<td>1</td>
</tr>
<tr>
<td>Skin, subcutaneous tissue, and breast</td>
<td>54</td>
<td>8,978</td>
<td>8</td>
</tr>
<tr>
<td>Eye</td>
<td>50</td>
<td>6,296</td>
<td>20</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>48</td>
<td>8,230</td>
<td>25</td>
</tr>
<tr>
<td>Male reproductive</td>
<td>46</td>
<td>6,868</td>
<td>11</td>
</tr>
<tr>
<td>Endocrine, nutritional, and metabolic</td>
<td>41</td>
<td>6,941</td>
<td>43</td>
</tr>
<tr>
<td>Circulatory</td>
<td>38</td>
<td>7,521</td>
<td>58</td>
</tr>
</tbody>
</table>

*The following MDCs were excluded: pregnancy (MDC14), newborn (MDC15), infectious and parasitic diseases (MDC18), alcohol/drug (MDC20), injury (MDC21), burns (MDC22), other factors (MDC23), and human immunodeficiency virus (MDC25).

### Comorbidity of 10 common conditions among UK primary care patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage who only have the row condition*</th>
<th>Mean No of conditions in people aged 65 years with row condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>8.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Stroke/transient ischaemic attack</td>
<td>6.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>14.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Painful condition</td>
<td>12.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Depression</td>
<td>25.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Dementia</td>
<td>5.3</td>
<td>4.1</td>
</tr>
</tbody>
</table>

* Percentage who do not have one of 39 other conditions in the full count

Guthrie B et al. BMJ 2012;345:bmj.e6341
Finding the “right mix” for each patient

RCT participants

GIM patients
Precision Medicine in 2018

McAlister et al. CMAJ 2017;189:E1065-E1068
Precision Medicine (2018): 

• Is an extension of traditional personalized care through more precise individualization of
  – diagnostic,
  – prognostic,
  – and therapy estimates

• for each patient by using sophisticated molecular diagnostics and/or imaging
Genomics

• Can screen for single gene diseases like HD, CF, Sickle cell anemia
  – NIH Health Genetic Testing Registry 51,519 genomic tests for 10,708 conditions

• Can identify pathogens in outbreaks (TB, C dif)

• Can identify people at higher risk for some cancers
  – BRCA1/2 and 16: www.cancergenome.nih.gov

• Genotype-guided prescribing
  – Colon cancer KRAS gene, breast cancer HER2 status, etc plus drugs targeting specific oncogenes
But some caveats about genomics

- Precision Oncology:
  - $5000 to $7500 US to sequence tumours
  - Applies to <2% of cancer patients

- Genotype-guided prescribing
  - Less than a dozen of over 350 gene-drug interactions have been endorsed by Office of Public Health Genomics in the CDC
  - Meta-analysis of 9 RCTs comparing genotype-guided (CYP2C9 gene) warfarin dosing vs. clinical dosing
    - Only 2812 patients!
TTR

INR > 4

Major Bleeding

Clots
…failed to show evidence of effect modification for breast cancer-free interval after tamoxifen treatment by CYP2D6 genotype
Whole genome sequencing

- NIH All of Us; 23 and Me; clinical care

But:
- Most diseases are multifactorial
- Most genetic variants have OR < 1.5 and add little to traditional prediction scores
- Some genetic variants indicate risk for diseases we don’t have Rx for (apoE4 and AD)
Whole genome sequencing

-Is anyone Normal?
-Could initiate harmful and/or costly diagnostic cascades

• 12 healthy volunteers
  ➢ 5 abN each
• ➢ 3 further tests each

Dewey et al. JAMA 2014;311:1035-1045
Unintended Consequences

Direct-to-consumer pharmacogenomic testing is associated with increased physician utilisation

Cinnamon S Bloss, Nicholas J Schork, Eric J Topol

ABSTRACT

Background: Direct-to-consumer (DTC) genomic testing has generated controversy, however the actual impact of testing on consumer behaviour has been understudied, particularly for pharmacogenomic (PGx) testing.

Methods: We recruited a sample of adults who purchased a DTC genomic test and had previously received their genomic test results for complex disease risk. All participants additionally underwent PGx testing.

Results: At follow-up, there were 481 PGx test recipients and 844 non-recipients still awaiting results. PGx test recipients had more physician visits (p=0.04) and were more likely to share their results with their physician (p=0.001). Both groups showed a decrease in anxiety symptoms from baseline to follow-up, with a trend for PGx recipients to show less of a decrease versus the typical small effect variants discovered for complex disease susceptibility.

Some have argued that PGx testing of variants with high predictive value does offer clear opportunities for clinical actionability. DTC PGx testing may also serve to raise public awareness of genomic analysis and its relevance to therapeutic drug response. Further, individuals taking relevant medications may be able to avoid suboptimal or adverse responses to those medications by leveraging their genetic information to guide drug selection and dosing. In contrast, however, DTC PGx testing has also been met with criticisms that are now familiar to the broader DTC genomic testing model. These include the fact that delivery does not involve a healthcare intermediary, that consumers may be confused or have poor psychological responses to the information provided, and that testing could potentially result in costly and unnecessary healthcare utilisation with little relative benefit. On this latter point, if care use is increased appropriately (eg, a patient finds they have a variant relevant to a drug they use), then this is presumably a good outcome. If, however, a patient makes appoint-

The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis

Gareth J Hollands, David P French, Simon J Griffin, Toby Prevost, Stephen Sutton, Sarah King, Theresa M Marteau

ABSTRACT

OBJECTIVE

To assess the impact of communicating DNA based disease risk estimates on risk-reducing health behaviours and motivation to engage in such behaviours.

DESIGN

Systematic review with meta-analysis, using Cochrane methods.

DATA SOURCES

The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis

BMJ. First published as 10.1136/bmj.l1102 on 18 December 2013. doi:10.1136/bmj.l1102

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Unanswered questions about precision omics:

• Will outcomes improve?
  – Just because we can measure a biomarker doesn’t mean using it will improve patient outcomes or costs of care
  – More than 90% of research on precision omics is basic science

  – Consider the GUIDE-IT Trial
High-Risk Heart Failure with Reduced EF
LVEF ≤ 40 within 12 months
HF event (hospitalization, ED visit, outpatient IV diuretics) within prior 12 mos
NT-proBNP > 2000 pg/mL within prior 30 days

Usual Care
N=550

Biomarker-Guided
NT-proBNP < 1000 pg/mL
N=550

Follow up: 2 wks, 6 wks, 3 months, then Q3 month for 12–24 mos

Additional 2-week follow-up after changes in therapy

Primary endpoint: Time to CV death or first HF hospitalization
Secondary endpoints:
• All-cause mortality
• Total days alive and out of hospital during follow-up
• CV mortality or CV hospitalization
• Safety
• Health-related quality of life
• Resource utilization, costs, cost effectiveness
Primary Endpoint (HF hosp or CV death)

HR (CI) = 0.983 (0.791, 1.222)
P value = 0.875

Duration of follow-up: Median (25th, 75th)
Biomarker-guided: 15 (7, 24)
Usual care: 15 (7, 24)
Process of Care

- Clinic Visits (median): NT-proBNP-Guided 12 vs. Usual Care 10 (P=0.002)
- Adjustments to HF therapy (median): NT-proBNP-Guided 6 vs. Usual Care 4 (P<0.001)

Legend:
- Red: NT-proBNP-Guided
- Blue: Usual Care

SOURCE: Duke Clinical Research Institute
Unanswered questions about precision omics:

• Will outcomes improve?
• For all, or who would benefit most?
• What are the harms?
  – False positives and labelling effects
• What is the cost-effectiveness?
  – 59 precision med tests studied (20% cost-saving)
Omics are a growth industry

old systems biologist at the Dana-Farber Cancer Institute in Boston hopes to see a first, rough draft of all the interactions that the genome encodes. Actually, he would be happy with a subset, a catalogue of all the proteins that come together in pairs. “That's what we've been doing for the past 20 years, and we're almost there now,” he says.

By 'almost there' Vidal means that his and a few other labs have observed 10–15% of human protein–protein interactions, based on studies of cells genetically engineered to generate a signal when a pair of proteins comes together. Other researchers have been pursing the same goal by plucking proteins from crushed cells and seeing which others come along for the ride, scouring the literature and making computational predictions based on protein shapes and the behaviour of related molecules.

It has helped that, more than a decade after the first large-scale interactome study, researchers are finally starting...
The most important of the omics:

People have different personalities, resilience, and resources that influence how they will experience illness. So basically, a disease that can turn one person’s personal and family life upside down may not affect another person the same way at all.
And perhaps the forgotten omic:

8% of housestaff day vs. 40% of housestaff day

Block et al. J Gen Intern Med 2013
the rise of the iPatient

Culture Shock — Patient as Icon, Icon as Patient
Abraham Verghese, M.D.

On my first day as an attending physician in a new hospital, I found my house staff and students in the team room, a snug bunker filled with glowing monitors. Instead of sitting down to hear about the patients, I suggested we head out to see them. My team came willingly, though they probably felt that everything I would need to get up to speed on our patients — the necessary images, the laboratory results — was right there in the team room. From my perspective, the most crucial element wasn’t.

For the next few weeks, I ensured that we spent as little time as possible in the bunker. These were excellent residents who cared enormously about patients’ welfare. They enjoyed being shown common findings — white nails of liver disease, an accessory nipple, Dupuytren’s contracture, parotid enlargement, spider angiomas, café au lait spots, the paradoxical splitting of the second heart sound in left bundle-branch block, signs of pseudo-
Precision Medicine and GIM?

McAlister et al. CMAJ 2017;189:E1065-E1068
What are Predictive Analytics?

- Exposome, microbiome
  - Exome (proteomics, metabolomics, transcriptomics)
  - Pathophysiologic phenotype
  - Biomarkers
  - Patient phenotype (clinical manifestations of disease)
    - 1. Functional status
    - 2. Quality and quantity of life
    - 3. Response to treatment
    - 4. Adherence to treatment
Predictive Analytics

Lots and lots of data + machine learning
Predictive analytics aren’t perfect
Predictive Analytics in Health Care

- Readmissions are common, costly, and negatively impact quality and quantity of life for patients
- Parkland Health – 29 item algorithm to identify those HF pts at high risk for 30d R/A
- Intervention for high risk pts:
  - Patient education from multidisc team
  - Telephone call within 48 hours
  - HF clinic appt within 7 days
  - PCP appt within 2 weeks for non-HF issues
Thirty-day readmission rates by month.

aOR 0.73 (0.58-0.93)
ARR 5%, NNT 20

### Table 2
Thirty-day readmission rates: pre-intervention and post-intervention periods* for all patients by HF and control groups

<table>
<thead>
<tr>
<th>Patient type</th>
<th>Pre-intervention (%)</th>
<th>Post-intervention (%)</th>
<th>Difference (95% CI)</th>
<th>p Value</th>
<th>Adjusted OR† (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>26.2</td>
<td>21.2</td>
<td>5.0 (1.0 to 9.0)</td>
<td>0.01</td>
<td>0.73 (0.58 to 0.93)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AMI and PNA</td>
<td>15.5</td>
<td>16.7</td>
<td>−1.2 (−5.4 to 2.9)</td>
<td>0.56</td>
<td>1.09 (0.80 to 1.48)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

### Table 3

Outpatient intervention and odds of readmission (n=913 HF index admissions, n=228 patients receiving interventions)*

<table>
<thead>
<tr>
<th>Intervention category</th>
<th>N</th>
<th>Expected readmission rate†</th>
<th>Observed readmission rate</th>
<th>Observed/expected ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient intervention completion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolled, received 1 or 2 outpatient components</td>
<td>150</td>
<td>23.8</td>
<td>17.3</td>
<td>0.73 (0.51 to 0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Enrolled, received ≥3 outpatient components</td>
<td>27</td>
<td>21.2</td>
<td>7.4</td>
<td><strong>0.35 (0.00 to 0.85)</strong></td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

MADIT-II: 80% Survive Regardless of Intervention

- Do not benefit from intervention (14.2%)
- Benefit (5.6%)
- Survive regardless of the intervention (80%)
Predictive Analytics can Improve Value

Value = \frac{\text{Patient Experience} + \text{Outcomes}}{\text{Cost}}

- Tailoring Treatment to Risk
- Increased Consistency of Care
- Tailor Treatment to Patient Preference
- Avoid Treatment in Patients with No Benefit
Predictive Analytics in Health Care – not just biomarkers
What does the future hold?

“prediction is very difficult — especially about the future.”

» Neils Bohr
Wearable Sensor Data

1. Activity
2. Pulse
3. Sleep stages
4. Blood pressure
5. Cardiac Output
6. ECG
7. Stress
   - HRV
   - EDA
8. Respiration rate
9. Oxygen saturation
10. CO2 levels
11. Temperature
12. Hydration
13. Glucose (?)
Many apps like MyHeart Counts
Sensing the Shift in Health Care

- **Eye**
  - Glucose-sensing lens
  - Digital fundoscope
  - Smartphone visual-acuity tracking
  - Automated refractive error
  - Noninvasive intraocular pressure
- **Ear**
  - Smart hearing aids
  - Digital otoscope
- **Lung**
  - Home spirometry
  - Pulse oximetry
  - Inhaler use
  - Breath-based diagnostics
  - Breathing sounds
  - Environmental exposure
- **Blood**
  - Continuous glucose
  - Transdermal Hb
  - Pathogens (genomics-based)
  - PoC blood tests
- **Skin**
  - Temperature
  - Gross lesions
  - Pressure sensor (wound care)
  - Sweat chemistry
  - Cutaneous blood flow
- **Other sensors and monitors**
  - Pill-box and -bottle
  - Posture
  - Body position
  - Activity
  - Sleep
- **Bladder and urine**
  - Comprehensive urinalysis
  - STDs (genomic detection)
  - Diaper-based sensors
- **Brain and emotion**
  - Wireless mobile EEG
  - Seizure
  - Autonomic nervous activity
  - Head-impact sensor
  - Intracranial pressure (noninvasive)
  - Stress recognition (voice, respiration)
- **Heart and vascular**
  - Continuous BP tracking
  - Handheld ECG
  - Heart rhythm
  - Cardiac output
  - Stroke volume
  - Thoracic impedance (fluid)
- **Gastrointestinal**
  - Endoscopic imaging
  - Esophageal pH
  - Medication compliance
  - Fecal blood or bilirubin
  - Gut electrical activity
  - Chewing
- **Watching over one's health**
  - Pulse
  - BP
  - Temperature
  - Activity
  - Hydration
  - Sleep stages
  - Seizure
  - Respiration rate
  - O₂ saturation
  - Blood CO₂
  - Blood glucose
  - ECG (single-lead)
  - Cardiac output
  - Stroke volume
  - Stress:
  - Heart-rate variability
  - Electrodermal activity

Steinhubl et al Science Trans Med 2015
Planet of the phones

By 2020, 80% of adults will have a supercomputer in their pocket.
HFpEF: 46 prognostic biomarkers to define 3 clusters (pheno)

Next: drug effects in each cluster
Divergent Pathways for CV Disease Therapy

**CONVENTIONAL**

- **Treatment**
  - Maintain electrolytes
  - Anti-arrhythmic drugs
  - Beta-blockers
  - Diuretics
  - Anti-hypertensive drugs
  - Surgically Implanted Devices (LVAD, ICD, CRT)
  - Heart Transplant

- **Treatment Plan**
  - Target selection based on:
    - signs and symptoms
    - condition of the patient

- **Present Diagnosis**
  - physical exams (murmurs)
  - diagnostic tests (EKG, Echo, Stress test)
  - genetic testing

- **Symptoms**
  - Dyspnea
  - Fatigue
  - irregular heart beats
  - edema of feet
  - medical/family history

**PRECISION DRIVEN**

- **Treatment**
  - (1)
  - (2)

- **Treatment Plan**
  - Target selection based on:
    - identified patient-specific novel gene or novel pathway

- **Phenotypic screen**

- **Future Diagnosis**
  - iPSC-CMs (1)
  - iPSC-CMs (2)

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From: Towards Cardio-Precision medicine
Eur Heart J..2014
Precision Medicine and GIM

Predictive Analytics rather than bespoke therapies in 2018

McAlister et al. CMAJ 2017;189:E1065-E1068
Learning Objectives

1. To describe precision medicine

2. To review the current status of precision medicine efforts relevant to General Internal Medicine practice

3. To explore the potential benefits, and limits, of precision medicine in the practice of General Internal Medicine
William Osler (1849-1919)

“The GOOD physician treats the DISEASE; the GREAT physician treats the PATIENT who has the disease.”

Sir William Osler
Questions / Comments?

WE HAVE TO GO SOMEWHERE OUT OF REACH FROM TECHNOLOGY.

SCOTLAND
Parting Advice from Sir William Osler:

“Look wise, say nothing, and grunt. Speech was given to conceal thought”