The clinical problem
- Multiple active regimens for the treatment of most diseases
- Variation in response to therapy
- Unpredictable toxicity

With choice comes decision

Probabalistic data is enough
Many clinical interventions are based on increased probability of a problem occurring
- Insulin/oral diabetes drugs
- Statins
- Antihypertensives
Why focus on drugs?

- Adverse drug events are 5th leading cause of death in USA
  - Adverse drug events are heavily litigated
  - Many adverse drug events are predictable
- Modern treatments are expensive
- Opportunities to improve ‘value’
Adverse Drug Events
Potential for Pharmacogenomics to Decrease Risk

• An estimated **2 to 4 million** persons suffer from a serious, disabling, or fatal adverse drug event each year

• In the United States, adverse drug events cause over **700,000** emergency room visits each year

• Over **120,000** of those emergency room visits result in further hospitalization

• Approximately **100,000 deaths** per year attributed to adverse drug events

Institute for safe medication practices Quarter Watch 2012
Institute for safe medication practices Quarter Watch 2013
http://www.cdc.gov/MedicationSafety/Adult_AdverseDrugEvents.html

Emergency Department Visits by Adults for Psychiatric Medication Adverse Events

<table>
<thead>
<tr>
<th>Medication Category and Class</th>
<th>No. of Cases</th>
<th>Estimated Annual No. of Visits</th>
<th>% Proportion of Category Visits</th>
<th>Hospitalization Rate</th>
<th>Estimated Annual ED Visits per 10,000 Outpatient Prescription Visits, No. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedatives and anxiolytics</td>
<td>1371</td>
<td>30,707</td>
<td>NA</td>
<td>13.5</td>
<td>3.6 (3.2-4.1)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1076</td>
<td>25,377</td>
<td>NA</td>
<td>12.4</td>
<td>2.4 (2.1-2.7)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1055</td>
<td>21,578</td>
<td>NA</td>
<td>15.3</td>
<td>11.7 (10.1-13.2)</td>
</tr>
<tr>
<td>Lithium salts</td>
<td>167</td>
<td>3620</td>
<td>NA</td>
<td>53.6</td>
<td>16.4 (13.0-19.9)</td>
</tr>
</tbody>
</table>

Estimated that ~ 90,000 patients visit ED each year due to psychiatric drug-induced adverse events

Hampton et al, *JAMA Psychiatry* 71(9); 2014
Why focus on drugs?

- Adverse drug events are 5th leading cause of death in USA
  - Adverse drug events are heavily litigated
  - Many adverse drug events are predictable
- Modern treatments are expensive
- Opportunities to improve ‘value’

THE PRECISION MEDICINE INITIATIVE

- Advance pharmacogenomics, the right drug for the right patient at the right dose
- Identify new targets for treatment and prevention
- Test whether mobile devices can encourage healthy behaviors
- Lay scientific foundation for precision medicine for many diseases
PERSONALIZED MEDICINE, SCHMERSONALIZED MEDICINE!

- Medicine has always been personalized

- Medicine is moving toward greater 'customer accountability'

- Medicine will never be personalized

- it is a change in expectation as well as some practical, process changes
Drivers of Precision Medicine

- Technology
  - Significant new opportunities over the past 5 years

- Patient financial burden
  - When you are paying more, you want more say

- Less personal care
  - Who will be my 'doctor' today?

- Cost of care
  - Even the USA can't afford treating 100% to benefit 20%
Pharmacogenomic examples-2016

- **bcr/abl or 9:22 translocation**—imatinib mesylate*
- **HER2-neu**—trastuzumab**
- C-kit mutations—imatinib mesylate**
- Epidermal growth factor receptor mutations—gefitinib
- BRAF-vemurafenib
- ALK-Crizotinib
- ROS-1_Crizotinib
- TPMT-mercaptopurine and azathioprine*
- UGT1A1-irinotecan**
- CYP2C9/VKORC1-warfarin*
- HLA-B*5701-abacavir
- HLA-B*1502-carbamazepine*
- IL28B-interferon
- CFTR-ivacaftor
- CYP2C19-clopidogrel, voriconazole
- CYP2D6-5-HT3 receptor antagonists, antidepressants, ADHD drugs, codeine derivatives*

Pain control
Antiemetics
Antidepressants
ADHD drugs
Anticoagulants
Not just tumor markers!!
**CPIC: Clinical Pharmacogenetics Implementation Consortium**

- The Clinical Pharmacogenetics Implementation Consortium (CPIC) is a shared project between PharmGKB and the Pharmacogenomics Research Network.
- CPIC guidelines are designed to help clinicians understand how genetic test results should be used to optimize drug therapy.
- Once published, the guidelines are updated periodically.

---

**CPIC Guidelines on PharmGKB**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>abacavir</td>
<td>CPIC Dosing Guidelines for abacavir and Atripla</td>
</tr>
<tr>
<td>allopurinol</td>
<td>CPIC Dosing Guidelines for allopurinol and HLA-B</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>CPIC Dosing Guidelines for amitriptyline and CYP2D6</td>
</tr>
<tr>
<td>azathioprine</td>
<td>CPIC Dosing Guidelines for azathioprine and TNF-Ti</td>
</tr>
<tr>
<td>captopril</td>
<td>CPIC Dosing Guidelines for captopril, Warner, Legler, and CPICD</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>CPIC Dosing Guidelines for carbamazepine and HLA-B</td>
</tr>
<tr>
<td>clonazepam</td>
<td>CPIC Dosing Guidelines for clonazepam and CYP2D6</td>
</tr>
<tr>
<td>clopidogrel</td>
<td>CPIC Dosing Guidelines for clopidogrel and CYP2D6</td>
</tr>
<tr>
<td>codeine</td>
<td>CPIC Dosing Guidelines for codeine and CYP2D6</td>
</tr>
<tr>
<td>desipramine</td>
<td>CPIC Dosing Guidelines for desipramine and CYP2D6</td>
</tr>
<tr>
<td>digoxin</td>
<td>CPIC Dosing Guidelines for digoxin and CYP2D6</td>
</tr>
<tr>
<td>fluvastatin</td>
<td>CPIC Dosing Guidelines for fluvastatin, Warner, Legler, and CPICD</td>
</tr>
<tr>
<td>imipramine</td>
<td>CPIC Dosing Guidelines for imipramine and CYP2D6</td>
</tr>
<tr>
<td>mesna</td>
<td>CPIC Dosing Guidelines for mesna and CYP2D6</td>
</tr>
<tr>
<td>nortriptyline</td>
<td>CPIC Dosing Guidelines for nortriptyline and CYP2D6</td>
</tr>
<tr>
<td>peginterferon alpha-2a</td>
<td>CPIC Dosing Guidelines for peginterferon alpha-2a, peginterferon alpha-2b, ramucirumab and P14.1 diabetes and HLA-B</td>
</tr>
<tr>
<td>peginterferon alpha-2b</td>
<td>CPIC Dosing Guidelines for peginterferon alpha-2b, peginterferon alpha-2a, ramucirumab and P14.1 diabetes and HLA-B</td>
</tr>
<tr>
<td>ribavirin</td>
<td>CPIC Dosing Guidelines for ribavirin and CYP2D6</td>
</tr>
<tr>
<td>sirolimus</td>
<td>CPIC Dosing Guidelines for sirolimus and LC0181</td>
</tr>
<tr>
<td>tegafur</td>
<td>CPIC Dosing Guidelines for tegafur, Warner, Legler, and CPICD</td>
</tr>
<tr>
<td>thioguanine</td>
<td>CPIC Dosing Guidelines for thioguanine and TNF-Ti</td>
</tr>
<tr>
<td>trimethoprim</td>
<td>CPIC Dosing Guidelines for trimethoprim and CYP2D6</td>
</tr>
<tr>
<td>warfarin</td>
<td>CPIC Dosing Guidelines for warfarin and CYP2D6</td>
</tr>
</tbody>
</table>
REASONS FOR PRECISION MEDICINE

- Testing for avoidance
- Testing for inclusion
- Testing for stratification
- Testing for explanation

Opiate Pharmacogenomics

Fig. — Metabolic pathways of commonly used opioids.
5-HT\textsubscript{3} Receptor Antagonists

<table>
<thead>
<tr>
<th></th>
<th>Primary pathway</th>
<th>Secondary pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrodolasetron (active</td>
<td>CYP2D6</td>
<td>CYP3A</td>
</tr>
<tr>
<td>metabolite of dolasetron)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granisetron</td>
<td>CYP3A</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>CYP3A4</td>
<td>CYP1A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP2D6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP2E1</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>CYP2D6</td>
<td>CYP3A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP1A1/2</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>CYP2D6</td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>

Ho K and Tong JG. *Current Opinion in Anaesthesiology* 2006, 19:606–611

Something for most everyone

Van Driest et al *Clin Pharmacol Ther* 2014
More discovery needed

- Relatively few precision medicine GWAS or NGS
- Replication data sets are difficult to obtain
- Team science is required
- Can’t ignore cost

CALGB 90401
Randomized Double-Blinded Placebo-Controlled Phase III Trial Comparing Docetaxel and Prednisone with and without Bevacizumab in Men with Hormone Refractory Prostate Cancer

Dan Hertz, Jai Patel, Kouros Owzar, Susan Dorsey, Eileen Dolan, Michael Morris, Kevin Kelly, Mark Ratain, Howard McLeod

Hormone refractory prostate cancer patients
Chemotherapy & anti-angiogenesis therapy naïve

21 day cycle

**ARM A**
- Docetaxel 75mg/m² IV on day 1 of each cycle
- Placebo IV on day 1 of each cycle
- Prednisone & dexamethasone

**ARM B**
- Docetaxel 75mg/m² IV on day 1 of each cycle
- Bevacizumab 15mg/kg IV on day 1 of each cycle
- Prednisone & dexamethasone

Patients treated maximum of two years or until disease progression, death, or severe toxicity

Kelly et al. J Clin Oncol 2012
90401 Consort

- Randomized on CALGB 90401 (n=1,050)
- Did not Register for PGx Substudy (n=186)
- Registered to PGx Substudy (n=864)
- No consent or not genotyped (n=74)
- Successful GWAS Performed (n=790)
- Genetically Defined European for Discovery (n=623)
- Genetically Defined non-European (n=167)

Toxicity Endpoints and Competing Risks in 90401 cohort (n=810)

<table>
<thead>
<tr>
<th>Docetaxel Toxicities</th>
<th>Bevacizumab Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Hypertension</td>
</tr>
<tr>
<td>1+</td>
<td>2+</td>
</tr>
<tr>
<td>285</td>
<td>57</td>
</tr>
<tr>
<td>36%</td>
<td>3%</td>
</tr>
<tr>
<td>161</td>
<td>6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity Endpoint</th>
<th>Completed tx w/o toxicity</th>
<th>Death/Progression</th>
<th>Tx Terminating Adverse Event</th>
<th>withdrew/other</th>
</tr>
</thead>
<tbody>
<tr>
<td>285</td>
<td>2%</td>
<td>31%</td>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td>36%</td>
<td>3%</td>
<td>37%</td>
<td>26%</td>
<td>14%</td>
</tr>
<tr>
<td>161</td>
<td>4%</td>
<td>40%</td>
<td>34%</td>
<td>17%</td>
</tr>
<tr>
<td>57</td>
<td>3%</td>
<td>36%</td>
<td>32%</td>
<td>17%</td>
</tr>
<tr>
<td>11%</td>
<td>4%</td>
<td>38%</td>
<td>34%</td>
<td>18%</td>
</tr>
<tr>
<td>34</td>
<td>3%</td>
<td>38%</td>
<td>36%</td>
<td>18%</td>
</tr>
<tr>
<td>4%</td>
<td>3%</td>
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<td>38%</td>
<td>18%</td>
</tr>
<tr>
<td>44</td>
<td>3%</td>
<td>38%</td>
<td>36%</td>
<td>18%</td>
</tr>
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<td>6%</td>
<td>4%</td>
<td>39%</td>
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<td>18%</td>
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<td>10</td>
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<td>1%</td>
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<td>38%</td>
<td>18%</td>
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<tr>
<td>53</td>
<td>3%</td>
<td>39%</td>
<td>38%</td>
<td>18%</td>
</tr>
<tr>
<td>7%</td>
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<tr>
<td>6%</td>
<td>3%</td>
<td>39%</td>
<td>38%</td>
<td>18%</td>
</tr>
<tr>
<td>49</td>
<td>3%</td>
<td>39%</td>
<td>38%</td>
<td>18%</td>
</tr>
<tr>
<td>6%</td>
<td>3%</td>
<td>39%</td>
<td>38%</td>
<td>18%</td>
</tr>
<tr>
<td>79</td>
<td>3%</td>
<td>39%</td>
<td>38%</td>
<td>18%</td>
</tr>
<tr>
<td>10%</td>
<td>3%</td>
<td>39%</td>
<td>38%</td>
<td>18%</td>
</tr>
</tbody>
</table>

- Prioritize GWAS by:
  - Clinical relevance of toxicity
  - Toxicity event rate
    - Note: half of patients received bevacizumab
  - Likelihood of genetic causal factor
  - Absence of strong confounding
Phenotype Cleaning for Competing Risks Analysis

- Distinct dataset for each toxicity endpoint GWAS
  - Categorize patients for toxicity of interest or treatment completion
  - Patients who discontinued treatment without experiencing toxicity endpoint categorized by reason for discontinuation (competing risk)
    - Death or progression
    - Treatment terminating adverse event (TTAE)
    - Withdrawal/other
- Each toxicity or competing risk assigned dose-at-event

CALGB 90401 Pharmacogenomic Substudy

- Aim
  - Discover loci that modulate toxicity risk in prostate cancer patients treated with docetaxel ± bevacizumab
- Separate GWAS for each toxicity of interest
  - Docetaxel: neuropathy, neutropenia
  - Bevacizumab: hypertension, proteinuria, hemorrhage, thrombosis
- Use dose-to-event Cox proportional hazards model for subdistributions
  - Cumulative docetaxel dose (mg/m²) at grade 3+ sensory neuropathy occurrence
  - Adjust for relevant clinical covariates
    - Age (continuous)
    - Diabetes (yes vs. no)
    - BMI (>30 kg/m² vs. other)
    - Treatment arm (bevacizumab vs. placebo)
Competing Risks Analysis

A 90401 subject treated with docetaxel

Experience neuropathy at docetaxel dose X

Complete 2 years of docetaxel w/o neuropathy

Estimate risk of docetaxel-induced neuropathy

Discontinue Docetaxel Treatment

Account for risk of competing event with a competing-risks analysis

Disease progression

Death

Severe toxicity

Study withdrawal

Cumulative Incidence of Neuropathy

Cumulative Incidence

Dose Since Start of Treatment (mg/m²)
Neuropathy GWAS

- 810 Subjects consented and genotyped on Illumina 610 quad
  - Discovery in 623 genetically defined European patients
  - 187 patient replication cohort (genetically defined non-European)
- No SNP reached genome-wide significance before adjustment
- Created priority SNP list based on:
  - P-value/rank
  - Biological plausibility
    - Previously reported associations
    - Gene function
    - LD with functional variant
    - Regulation of gene expression
    - Encode data
### Neuropathy GWAS Priority SNPs

<table>
<thead>
<tr>
<th>Rank</th>
<th>rsID</th>
<th>Gene</th>
<th>MAF</th>
<th>P-value</th>
<th>Adj p-val</th>
<th>HR</th>
<th>Plausible Biological Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rs11017056</td>
<td>-</td>
<td>0.22</td>
<td>4.7E-7</td>
<td>7.2E-8</td>
<td>2.83</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>rs875858</td>
<td>VAC14</td>
<td>0.06</td>
<td>7.7E-7</td>
<td>1.6E-6</td>
<td>3.43</td>
<td>Stabilizes FIG4 → causes CMT</td>
</tr>
<tr>
<td>3</td>
<td>rs10761189</td>
<td>FGD3</td>
<td>0.40</td>
<td>3.1E-6</td>
<td>5.3E-6</td>
<td>2.32</td>
<td>Functionally related to FGD4 (40101)</td>
</tr>
<tr>
<td>7</td>
<td>rs1027796</td>
<td>OPCML</td>
<td>0.30</td>
<td>4.8E-6</td>
<td>8.3E-6</td>
<td>2.29</td>
<td>Neuronal outgrowth &amp; connectivity (CNS)</td>
</tr>
<tr>
<td>15</td>
<td>rs17185211</td>
<td>DOK6</td>
<td>0.23</td>
<td>1.1E-5</td>
<td>3.4E-5</td>
<td>2.30</td>
<td>Highly expressed in the developing CNS</td>
</tr>
<tr>
<td>26</td>
<td>rs478472</td>
<td>NAV1</td>
<td>0.08</td>
<td>1.7E-5</td>
<td>2.2E-5</td>
<td>3.25</td>
<td>Relevant to neuronal development</td>
</tr>
<tr>
<td>72</td>
<td>rs12805206</td>
<td>OPCML</td>
<td>0.22</td>
<td>7.6E-5</td>
<td>1.3E-4</td>
<td>2.33</td>
<td>Neuronal outgrowth &amp; connectivity (CNS)</td>
</tr>
</tbody>
</table>

Hertz et al Clin Cancer Res in press
Assessing the VAC14 ‘hit’

Hertz et al Clin Cancer Res in press
More discovery needed

- Relatively few precision medicine GWAS or NGS
- Replication data sets are difficult to obtain
- Team science is required
- Can’t ignore cost

Assessing the VAC14 ‘hit’

Mean Withdrawal Thresholds

VAC14 +/- mice

Hertz et al Clin Cancer Res in press
**Docetaxel vs. Paclitaxel**  
(Clinical data: SCOTROC1)

**Accrual of 1077 Pts With:**  
- Stage IC-IV epithelial ovarian cancer  
- ECOG PS 0-2  
- No prior history of CT or RT  

**RANDOMISATION**

- Docetaxel 75 mg/m² 1-hr IV, followed by Carboplatin AUC 5' IV  
- Paclitaxel 175 mg/m² 3-hr IV, followed by Carboplatin AUC 5' IV  
- Repeat q 3 wk for up to 6 cycles  
- Repeat q 3 wk for up to 6 cycles

**Study End Points**  
**Primary:** progression-free survival  
**Secondary:** response rate, overall survival, toxicity, QOL

Sarah Glass, Alison Motsinger-Reif, Sharon Marsh, Bob Brown, Jim Paul

---

**Docetaxel vs. Paclitaxel**  
(Clinical data: SCOTROC1)

**Progression-free survival**

**Overall survival**

Vasey et al JNCI 2004
Chemotherapy Neurotoxicity: Candidate Gene Approach

The filtering of Neuro-risk genotypes

Figure 1: The workflow of the data analysis, represented by the narrowing number of SNPs at each stage of the analysis.
Table 1: SNPs significantly associated with severe neurotoxicity in the validation cohort

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Base Change</th>
<th>Corrected P-value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Risk Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs139887</td>
<td>SOX10</td>
<td>C-&gt;G</td>
<td>0.001</td>
<td>2.87</td>
<td>(1.4361, 5.7530)</td>
<td>CG</td>
</tr>
<tr>
<td>rs2849380</td>
<td>BCL2</td>
<td>A-&gt;G</td>
<td>0.013</td>
<td>4.08</td>
<td>(1.5254, 10.8975)</td>
<td>AA</td>
</tr>
<tr>
<td>rs544093</td>
<td>OPRM1</td>
<td>A-&gt;C</td>
<td>0.015</td>
<td>2.25</td>
<td>(1.2365, 4.0841)</td>
<td>AA</td>
</tr>
<tr>
<td>rs879207</td>
<td>TRPV1</td>
<td>A-&gt;G</td>
<td>0.002</td>
<td>2.31</td>
<td>(1.4467, 3.6767)</td>
<td>AG</td>
</tr>
</tbody>
</table>

Table 2: Percent PAR for each SNP and joint PAR

<table>
<thead>
<tr>
<th>SNP</th>
<th>PAR (%)</th>
<th>PAR (%)</th>
<th>PAR (%)</th>
<th>PAR (%)</th>
<th>PAR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs139887</td>
<td>45.8</td>
<td>rs2849380</td>
<td>9.1</td>
<td>rs544093</td>
<td>50.2</td>
</tr>
<tr>
<td>rs879207</td>
<td>38.4</td>
<td>All SNPs</td>
<td>84.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Neuro-risk genotypes not associated with outcome
Peripheral Neuropathy Pharmacogenetics is peripheral neuropathy biology

**FGD4, EPHA5, FZD3**

**ARHGEF10, PRX**

**RXF2**

**Axon outgrowth genes**

Polygenic inheritance of paclitaxel-induced sensory peripheral neuropathy driven by axon outgrowth gene sets in CALGB 40101 (Alliance)

More discovery needed

- Relatively few precision medicine GWAS or NGS
- Replication data sets are difficult to obtain
- Team science is required
- Can’t ignore cost
**VORICONAZOLE AND CYP2C19: CLINICAL IMPLICATIONS**

- Used to treat fungal infection
- Used as fungal prophylaxis in myeloid malignancies

28% of patients with "high-risk" CYP2C19 genotypes that would require a dose modification or a different medication

Dr Gillian Bell, Moffitt Cancer Center
Genotyping for Ultrarapid Metabolizers in Adult BMT and AML Patient Populations Can Save Significant Healthcare Costs

Realistic Case

Cost Savings Model Based on 100 Patients

<table>
<thead>
<tr>
<th></th>
<th># of Patients</th>
<th>Cost of Genotyping</th>
<th>Incremental Savings by Avoiding IFI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of Screening Patients</td>
<td>100</td>
<td>($319.12)</td>
<td>-</td>
<td>($31,912)</td>
</tr>
<tr>
<td>Cost Savings from Genotyping</td>
<td>5</td>
<td>-</td>
<td>$29,183</td>
<td>$145,915</td>
</tr>
<tr>
<td>Total Cost Savings from CYP2C19 Screening Program</td>
<td></td>
<td></td>
<td>$114,003</td>
<td></td>
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<tr>
<td>Total Savings/Patient</td>
<td></td>
<td></td>
<td>$1,140</td>
<td></td>
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</tbody>
</table>

Assumptions:
- Estimated # of Patients with CYP2C19*17 = 30
- Predicted # of Patients to Develop IFI = 5.4
- Estimated Effectiveness of CYP2C19*17 Status Based Intervention = 94%
- Estimated # of IFI Cases Avoided by Genotyping = 5.4 x 0.94 = 5

Moffitt Cancer Center 2016

Cancer Pharmacogenomics and Tumor and Germline Genomes.

Practical choices

- Selection from amongst ‘equals’
- Clinical trial options, beyond non-specific or anatomical
- ‘acceptable’* levels of toxicity
- *to the patient, not prescriber

Cancer Care is changing fast: the opportunity and the threat
Recent example

55 yo female, Stage IV leiomyosarcoma spread to the lungs

Previous therapy in addition to surgical excision includes:

* Gemcitabine and docetaxel x 3 months then
* Doxorubicin and ifosfamide x 4 months then
* Dacarbazine and gemcitabine x 3 months then
* Pazopanib x 3 months but is no longer working

No clear next steps and patient is fit and wants to keep trying
Patient enrolled on MCC 17148 with the anti-PD-L1 monoclonal antibody MEDI4739 at the very end of August 2014

Options that had not been previously visible

**Histology-Based Clinical Trial Design to Evaluate Multiple Molecular Aberrations**

"Umbrella Trial"

- Variety of targeted agents
- Specific molecular profiles
- Single tumor type

DeBartolo Family
PERSONALIZED MEDICINE INSTITUTE
**HISTOLOGY-INDEPENDENT, ABERRATION-SPECIFIC CLINICAL TRIAL DESIGN**

“Basket Trial”

Eligibility is based on molecular aberrations rather than anatomical origin of a cancer.

---

**Cancer Pharmacogenomics and Tumor and Germline Genomes.**

Some ‘other’ genomes

Melting pot or carton of eggs?

Number of Participants and Approvals Captured with Racial Data

<table>
<thead>
<tr>
<th></th>
<th>1997</th>
<th>2004</th>
<th>2009</th>
<th>2012</th>
<th>TOTAL</th>
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</thead>
<tbody>
<tr>
<td>CNS</td>
<td>6,902 (5)</td>
<td>6,847 (6)</td>
<td>5,189 (3)</td>
<td>3,810 (3)</td>
<td>22,748 (17)</td>
</tr>
<tr>
<td>CV</td>
<td>28,031 (6)</td>
<td>5,360 (3)</td>
<td>35,786 (9)</td>
<td>19,702 (4)</td>
<td>88,879 (22)</td>
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<tr>
<td>Oncology</td>
<td>3,353 (5)</td>
<td>2,773 (7)</td>
<td>1,310 (5)</td>
<td>6,883 (12)</td>
<td>14,319 (29)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>38,286 (16)</td>
<td>14,980 (16)</td>
<td>42,285 (17)</td>
<td>30,395 (19)</td>
<td>127,175 (68)</td>
</tr>
</tbody>
</table>

Knepper et al, unpublished
How has the number of countries hosting investigator sites changed?

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Total Countries</td>
<td>31</td>
<td>43</td>
<td>56</td>
<td>61</td>
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<tr>
<td>Unique Countries</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>19</td>
</tr>
</tbody>
</table>

Knepper et al, unpublished

World Maps

Knepper et al, unpublished
Racial Composition of Approvals from All Clinical Areas

Racial Composition of Pivotal Trials in 1997
- Caucasian (90.98%)
- Black (2.88%)
- Asian (0.15%)
- Hispanic (0.13%)

Racial Composition of Pivotal Trials in 2004
- Caucasian (87.17%)
- Black (5.37%)
- Asian (1.55%)
- Hispanic (1.40%)

Racial Composition of Pivotal Trials in 2009
- Caucasian (84.13%)
- Black (6.78%)
- Asian (4.10%)
- Hispanic (3.22%)

Racial Composition of Pivotal Trials in 2012
- Caucasian (82.15%)
- Black (3.74%)
- Asian (12.64%)
- Hispanic (1.33%)

Knepper et al, unpublished

Average predicted warfarin weekly dose
Risk of GI toxicity to amodiaquine
Risk of Simvastatin myotoxicity

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### Practical choices

- Selection from amongst ‘equals’
- Clinical trial options, beyond non-specific or anatomical
- ‘acceptable’* levels of toxicity

*to the patient, not prescriber
Translational science: The steps to success

- Step I: Discovery
- Step II: Validation
- Step III: Integration into practice
- Step IV: Integration into policy
ACKNOWLEDGEMENTS

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