PERSONALIZED MEDICINE FOR VHL AND OTHER HEREDITARY RENAL MALIGNANCIES

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

With choice comes decision

Lot’s of options for kidney cancer

immunotherapy
IL-2
Kinase inhibitors
Antivascular agents
chemotherapy

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

- Cancer chemotherapy is expensive

- Opportunities to improve ‘value’
Pharmacogenomic examples - 2017

- 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
- 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, and codeine derivatives*

Pain control
Antiemetics
Antidepressants
ADHD drugs
Anticoagulants
Not just tumor markers!!

Cancer Care is changing fast: the opportunity and the threat

Practical choices
- Selection from amongst ‘equals’
- Clinical trial options, beyond non-specific or anatomical
- ‘acceptable’* levels of toxicity
- *to the patient, not prescriber
Recent example
55 yo female, Stage IV clear cell renal cancer spread to the lungs
Previous therapy in addition to surgical excision includes:
*Gemcitabine/Sunitinib x 4 months then
*Everolimus 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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Mutation</th>
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</table>

Patient enrolled on PARP inhibitor clinical trial with stable disease since August 2016
Options that had not been previously visible
**VHL Mediated Target Activation**

- Endothelial cell proliferation & survival
- Autocrine stimulation of KDR
- Suppression of anti-tumor immune response
- Autocrine stimulation of mTOR
- Stimulation of mTOR
- EGFR
- Stimulation of EGFR
- TGF-α
- Endothelial cell proliferation & Metastasis
- Suppression of anti-tumor immune response
- Pericyte proliferation & survival
- MMPs
- Breakdown of ECM
- Angiogenesis
- CXCR4
- Stimulation of CXCR4
- RGP-1
- Angiogenesis

**Opiate Pharmacogenomics**

- Codeine
- Morphine
- Hydrocodone
- Hydromorphone
- Fentanyl
- Tropisetron

**5-HT3 Receptor Antagonists**

<table>
<thead>
<tr>
<th>Primary pathway</th>
<th>Secondary pathway</th>
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<tr>
<td>Hydrodolasetron (active metabolite of dolasetron)</td>
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<td>Granisetron</td>
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</tbody>
</table>

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

Clinical Risk Panel: easier to test all than some

- Clinical pathway-driven care
- Adhere to cancer risk guidelines
- Identify underlying predisposition to severe toxicity
- Mitigating risk of untoward drug effects
- Enriching for probability of benefit

Growing number of 'actionable' genes

A Broader Strategy

- Neuropathy risk
- Cardiotoxicity risk
- Bone marrow 'opathy' risk
- Gastropathy risk
- Hereditary cancer risk
- Eligibility for PARP inhibitors
- Criteria for immunotherapy
- Drug selection and dosing
  - Pain control
  - Antiemetics
  - Antifungals
  - Anesthesia risks
  - Coagulation risks

Cancer Pharmacogenomics and Tumor and Germline Genomes.

- Some 'other' genomes

Practical choices

- Selection treatment from amongst 'equals'
- Clinical trial options, beyond non-specific or anatomical
- Longitudinal monitoring for futility/next options
- 'acceptable'* levels of toxicity
  - We have to ask!
  - *to the patient, not prescriber
- Preemptive assessment of benefit:risk, to AVOID risk and ASSURE the best change of benefit