Genome variation affecting predisposition and response to therapy

Tom Hudson, MD
President and Scientific Director
Ontario Institute for Cancer Research
Outline

• Genome-wide analyses of colon cancer and risk prediction;

• Multiplexed genome analyses of tumors in clinical trials and disease management.
**rs10505477 (8q24 locus)**

*First CRC genetic marker validated in > 10,000 subjects*

<table>
<thead>
<tr>
<th>Population</th>
<th>OR</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ontario</td>
<td>1.22</td>
<td>0.058</td>
</tr>
<tr>
<td>Seattle/Newfoundland</td>
<td>1.11</td>
<td>0.087</td>
</tr>
<tr>
<td>Scotland3</td>
<td>1.22</td>
<td>0.066</td>
</tr>
<tr>
<td>Scotland4</td>
<td>1.16</td>
<td>0.046</td>
</tr>
<tr>
<td>France/Nantes</td>
<td>1.13</td>
<td>0.060</td>
</tr>
<tr>
<td>France/Familial</td>
<td>1.28</td>
<td>0.099</td>
</tr>
<tr>
<td>EPIC</td>
<td>1.13</td>
<td>0.072</td>
</tr>
<tr>
<td><strong>Summary-All</strong></td>
<td>1.17</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>French/EPIC only</strong></td>
<td>1.16</td>
<td>0.042</td>
</tr>
</tbody>
</table>

**Odds ratios for log-additive model**

Lessons learned from hundreds of common variants associated with cancer using GWAS:

1. Odds ratios are low (1.1-1.4).
2. Few new genes identified (KLK3/Prostate Specific Antigen, nicotinic acetylcholine receptor subunit genes on 15q25).
3. Some loci seen in multiple cancers (8q24/MYC, TERT-CLPTM1L).
4. When known, causal alleles often implicate regulatory mechanisms.
5. Most loci not understood.
6. **FUNCTIONAL ANALYSES AT GWAS LOCI NEEDED!**
Risk versus CRC-allele count

Houlston et al, Nat Genet, 2008

<table>
<thead>
<tr>
<th>Number of risk alleles</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=4</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>5</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>6</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>7</td>
<td>7%</td>
<td>11%</td>
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<td>8</td>
<td>14%</td>
<td>17%</td>
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<td>9</td>
<td>19%</td>
<td>20%</td>
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<td>10</td>
<td>20%</td>
<td>18%</td>
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<td>11</td>
<td>17%</td>
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<tr>
<td>12</td>
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<tr>
<td>13</td>
<td>5%</td>
<td>3%</td>
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<td>14</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>&lt;=15</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
ORIGINAL ARTICLE

Cumulative impact of common genetic variants and other risk factors on colorectal cancer risk in 42,103 individuals

Malcolm G Dunlop,1 Albert Tenesa,2 Susan M Farrington,1 Stephane Ballereau,1 David H Brewster,3 Thibaud Kossler,4 Paul Pharoah,4 Clemens Schafmayer,5 Jochen Hampe,6 Henry Völzke,7 Jenny Chang-Claude,8 Michael Hoffmeister,8 Hermann Brenner,9 Susanna von Holst,10 Simone Picelli,10 Annika Lindblom,10 Mark A Jenkins,11 John L Hopper,11 Graham Casey,12 David Duggan,13 Polly A Newcomb,14 Anna Abulí,15 Xavier Bessa,15 Clara Ruiz-Ponte,16 Sergi Castelví-Bel,17 Iina Niittymäki,18 Sari Tuupanen,18 Auli Karhu,18 Lauri Aaltonen,18 Brent Zanke,19 Tom Hudson,20 Steven Gallinger,21 Ella Barclay,22 Lynn Martin,22 Maggie Gorman,22 Luis Carvajal-Carmona,22 Axel Walther,22 David Kerr,23 Steven Lubbe,24 Peter Broderick,24 Ian Chandler,24 Alan Pittman,24 Steven Penegar,24 Harry Campbell,25 Ian Tomlinson,22 Richard S Houlston24

Gut (2012)

**Males**

![Graph showing the absolute 10-year risk for different genotypes in males.]

**Females**

![Graph showing the absolute 10-year risk for different genotypes in females.]

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OICR

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7
Cancer
A disease of the genome

Challenge in treating cancer:
- Every tumour is different;
- Every cancer patient is different.

Lessons learned from cancer genome research:
- Heterogeneity within and across tumour types;
- High rate of abnormalities (driver vs. passenger);
- Sample quality matters.
The rise of sequencing technologies, cancer genomics, and targeted therapeutics:

A perfect storm!

Implications for Personalized Medicine
Dramatic increases in sequencing throughput since the Human Genome Project...

... have resulted in > 100,000-fold decreases in sequencing costs:

• $1,000/genome will soon be achieved
ICGC Map - September 2012

47 projects launched
Successful targeted drug development

Cancer drugs and genomic alterations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Genetic Marker</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib, Dasatinib, Nilotinib</td>
<td>BCR-ABL</td>
<td>• Ph+ CML</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ph+ ALL</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF V600E</td>
<td>• Melanoma</td>
</tr>
<tr>
<td>Olaparib, Valiparib, Iniparib</td>
<td>BRCA1/2</td>
<td>• Ovarian and breast cancer with BRCA mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Triple-negative breast cancer</td>
</tr>
<tr>
<td>Imatinib</td>
<td>c-Kit</td>
<td>• Kit (CD117) positive malignant GIST</td>
</tr>
<tr>
<td>Erlotinib, Gefitinib</td>
<td>EGFR</td>
<td>• Advanced/metastatic NSCLC</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2 amplification</td>
<td>• HER2 (+) breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HER2 (+) gastric or GEJ cancer</td>
</tr>
<tr>
<td>Cetuximab, panitumumab</td>
<td>KRAS</td>
<td>• Wild-type KRAS colon cancer</td>
</tr>
</tbody>
</table>

Hundreds in development
Surveys of mutation databases indicate that most mutations are found in many tumour types

Sanger Institute: http://www.sanger.ac.uk/cosmic, COSMIC v54 Release (Forbes et al., 2011).
How are we currently using genomics in patient management?

**Single Gene Alteration**

- Already incorporated in patient management;
- Impacts the following decisions:
  - Selection of agents:
    - Positive effect;
    - Negative effect.
  - Prediction of toxicity;
  - Treatment changes in case of resistance.

**Multiple gene alterations**

- Under investigation at many institutions;
- Should it be incorporated in routine care or remain a research tool?
- Is it practical?
- What is the cost/benefit?
Mutations have different levels of importance in personalized medicine

• “Actionable”: genomic aberrations that have the potential to impact on treatment recommendations for predictive or prognostic reasons, or those with known prognostic or diagnostic implications;

• “Druggable”: genomic aberrations for which pharmaceutical agents are available or known to be in development;

• “Disease-associated”: genomic aberrations that correlate disease or drug response; most do not have demonstrated clinical impact.
Molecular by sequencing: the next frontier!

Single genes ↔ Gene panels ↔ Exomes ↔ Whole genomes

+ Gene expression profiles, copy number variation, etc.
Key questions regarding the implementation of cancer sequencing in the clinic

1. Is technology ready and reliable?
2. Can FFPE replace fresh tumour biopsies?
3. What are the differences between primary and metastatic sites?
4. Is turnaround of results acceptable for clinical use?
5. How to interpret and report the data?
6. Do we have enough targeted agents available?
7. How to design clinical trials to prove benefits?
8. How to handle incidental findings (heritable risks)?
Cancer Genomics and Bioinformatics Leaders: Drs. John McPherson and Lincoln Stein

**World class expertise & resources**

- Monthly capacity: >17 trillion bases and growing
- Instrumentation:
  - **Rapid sequencing:**
    - 1 Pacific Biosciences RS, 1 Illumina MiSeq, 1 Ion Torrent PGM
  - **Deep sequencing:**
    - 10 Illumina HiSeq 2000

**IT Specifications:**
- 8,000 cores
- 64 nodes with 192GB RAM
- 153 nodes with 16 GB RAM
- 224 nodes with 24 GB RAM
- 64 nodes with 96 GB RAM
- 5 nodes with 256 GB RAM
- 3.5PB of online storage
- 1Gb, 10Gb and fibre connectivity
**PacBio: Small molecule real time (SMRT™) DNA sequencing**

- Single molecule;
- Simple sample preparation
- Long reads (>=2kb);
- 30-40 minute run time;
- ~100Mb per run.

**Circular Consensus Sequencing:**

- Short templates can be sequenced multiple times;
- Increases accuracy;
- Ideal for PCR products.
OncoCarta Panel

Sequenom:
- 19 genes;
- 238 somatic mutations;
- 23 multiplex PCR pools.

PacBio (First 50 patients):
- 73 PCR amplicons;
- 70-100bp;
- Span 238 OncoCarta mutations.
Sequencing identifies known mutations

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Sequenom OncoCarta v.1 Screening Results</th>
<th>VRF (%)</th>
<th>DsX</th>
<th>PB CCS</th>
<th>Onco Carta</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBOT1</td>
<td>PIK3CA H1047L (24%)</td>
<td>8</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT2</td>
<td>NRAS G12D (92%)</td>
<td>98</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT3</td>
<td>PIK3CA E545K (36%)</td>
<td>11</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>PBOT4</td>
<td>no mutation</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBOT5</td>
<td>BRAF V600R (44%)</td>
<td>2</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT6</td>
<td>no mutation</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PBOT7</td>
<td>BRAF L597Q (28%)</td>
<td>18</td>
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<tr>
<td>PBOT8</td>
<td>EGFR L747_S752del, P753S</td>
<td>NA</td>
<td></td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>PBOT9</td>
<td>KRAS G13D (46%)</td>
<td>41</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT10</td>
<td>KRAS G12V (62%) + PIK3CA E545K (26%)</td>
<td>14 &amp; 10</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT11</td>
<td>KRAS G12S (68%)</td>
<td>92</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>PBOT12</td>
<td>KRAS G12V (43%)</td>
<td>8</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT13</td>
<td>no mutation</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBOT14</td>
<td>NRAS Q61R (42%)</td>
<td>32</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>PBOT15</td>
<td>KRAS Q61H (76%)</td>
<td>13</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>PBOT16</td>
<td>KIT V559_V560del (sequenom), V559D (seq)</td>
<td>6</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>PBOT17</td>
<td>PDGFR A842V (32%)</td>
<td>26</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT18</td>
<td>KIT W557G (48%) (sequenom), Trp557_Lys558del (seq)</td>
<td>NA</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT19</td>
<td>BRAF V600E (64%)</td>
<td>73</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT20</td>
<td>JAK2 V617F (18%)</td>
<td>4</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT21</td>
<td>EGFR L858R (23%)</td>
<td>4</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT22</td>
<td>no mutation</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBOT23</td>
<td>ABL1 E255K (48%)</td>
<td>60</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT24</td>
<td>no mutation (sequenom), KRAS G12D (by Dxs)</td>
<td>NA</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT25</td>
<td>AKT rs.34409589 Del (E17del, K missense) (50%)</td>
<td>71</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT26</td>
<td>KIT V560D (44%)+V560del (41%) (sequenom), V560D (seq)</td>
<td>14</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT27</td>
<td>PDGFR A843_D846del (35%)</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBOT28</td>
<td>KRAS G12D (23%)</td>
<td>2</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT29</td>
<td>PIK3CA H1047R (26%) + MET T992I (56%)</td>
<td>3 &amp; 31</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PBOT30</td>
<td>no mutation</td>
<td>NA</td>
<td></td>
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</tr>
</tbody>
</table>
Sequencing identifies new mutations

4% of ERBB2 coding region sequenced

Observed depth of coverage across ERBB2_chr17_37856254_37884914 (window size = 50bp).
Mean coverage is increasing
Sample Physician Report v2

Mutation Report for E746_A750del in EGFR

Description of the Gene

The EGFR (epidermal growth factor receptor) gene, also known as ERBB1, encodes the transmembrane receptor tyrosine kinase protein EGFR, which consists of an extracellular ligand binding domain and an intracellular tyrosine kinase domain. EGFR is activated following binding of extracellular ligands such as EGF. Activation of EGFR leads to downstream activation of the MAPK and PI3K pathways, resulting in cellular proliferation and survival. Ligand independent activation can occur as a result of activating mutations in the tyrosine kinase coding region within the EGFR gene. Common activating mutations in exon 19 and exon 21 of the EGFR gene are validated predictive biomarkers for benefit to EGFR targeted tyrosine kinase inhibitors (TKI). Additional mutations in exon 20 can cause structural changes to the EGFR protein and result in resistance to EGFR targeted TKIs. Downstream activating mutations in KRAS have been shown to predict for lack of benefit to EGFR targeted therapies in colorectal cancer.

Frequency of E746_A750del mutation in EGFR in the top tumour types

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Frequency</th>
<th>Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. lung carcinoma</td>
<td>0.3411</td>
<td>(1320/38714 samples)</td>
</tr>
<tr>
<td>2. breast carcinoma</td>
<td>0.2237</td>
<td>(1447 samples)</td>
</tr>
<tr>
<td>3. ovary carcinoma</td>
<td>0.3810</td>
<td>(2/525 samples)</td>
</tr>
<tr>
<td>4. salivary gland carcinoma</td>
<td>2.1646</td>
<td>(5231 samples)</td>
</tr>
<tr>
<td>5. thyroid carcinoma</td>
<td>1.6074</td>
<td>(7367 samples)</td>
</tr>
<tr>
<td>6. kidney carcinoma</td>
<td>1.4286</td>
<td>(2/140 samples)</td>
</tr>
<tr>
<td>7. upper aerodigestive tract carcinoma</td>
<td>0.2441</td>
<td>(3/1223 samples)</td>
</tr>
</tbody>
</table>

EGFR E746_A750del Characteristics

The functional consequence of this mutation is Activating | Reference (PMID): pmid:30887192

Clinical and Preclinical Studies

Clinical and Preclinical Studies

This mutation occurs in exon 17 of the activation loop of the kinase.

1. lung carcinoma 0.3411%

In this tumour type, the clinical significance of this mutation has been examined by PROSPECTIVE clinical trials.

Multiple large studies have demonstrated that EGFR exon 19 deletions, including E746_A750del is predictive for response to EGFR tyrosine kinase inhibitors including erlotinib and gefitinib.

Reference (PMID): pmid:20887192 Evidence: IA

2. breast carcinoma 0.2237%

In this tumour type, the clinical significance of this mutation is UNKNOWN.

Reference (PMID): Evidence:

Availability of Investigational Agents

The available Investigational agents EGFR tyrosine kinase inhibitors have documented efficacy Known Effective

Sensitivity and Resistance Conferred by Mutation

There are standard of care guidelines that suggest this mutation confers sensitivity to EGFR TKIs.

Report History

<table>
<thead>
<tr>
<th>Date</th>
<th>Confirmed by</th>
<th>Comment</th>
</tr>
</thead>
</table>


OICR/PMH Feasibility Study

**Objective:** To determine how to optimally use large-scale/genome-wide characterization of cancer genes and other genetic markers of susceptibility or resistance to cancer therapies.

<table>
<thead>
<tr>
<th>Eligible patients with biopsiable tumour</th>
<th>Bx</th>
<th>Pacific Biosciences Sequencing of “actionable” genome</th>
<th>Genomic information provided to investigators</th>
<th>Record application of genomic information and outcome</th>
</tr>
</thead>
</table>

**Key Eligibility**
- Advanced/recurrent or metastatic disease;
- Potential candidate for clinical trial;
- Biopsiable disease;
- Adequate organ function;
- Available archival tissue block or slides and whole blood sample for correlative studies and path review;
- Informed consent.

2011 Pilot = 50-80 subjects - funded
2012/2016 = 1000 subjects - not funded
Feasibility Study Results

• 117 patients enrolled March 2011 – September 2012/5 centres
  – Phase 2 – 4/2012-current 27/80 patients evaluated using Sequenom, MiSeq

• Analysis of initial 50 patients (Tran et al IJC Sept 2012 epub)

• Outputs: SOPs, bioinformatics, expertise, collaborations

• Current status: evaluating MiSeq, expanded gene panel to support large clinical genomics cohort study
Feasibility Study - Design

- Blood, tumor biopsy and archived samples were collected from advanced cancer patients recruited from 5 cancer centres.
- Samples were analyzed using 3 technologies: targeted exon sequencing using Pacific Biosciences PacBio RS next generation sequencer, multiplex somatic mutation genotyping using Sequenom MassARRAY.
- Actionable mutations were verified in a CAP/CLIA/OLA certified clinical laboratory using Sanger sequencing.
- Standardized reports were generated and sent to clinicians.
- Patients followed q 3 months x 2 years.
Feasibility criteria

✓ Acceptability
  (enroll $\geq 50\%$ of patients approached)

✓ Sample quality
  (provide sufficient DNA for analysis from $\geq 90\%$ of biopsy samples)

✓ Molecular analysis
  (successfully generate a molecular profile from a CLIA laboratory in $\geq 90\%$ of patients)

✓ Timeliness
  (generate a molecular profile $\leq 21$ days from consent)

✓ Utility
  (identify actionable mutations in $\geq 30\%$ of patients)
GPS – clinical summary of first 57 patients enrolled

• 5 Ontario sites activated;

• Enrolled first subject on March 21, 2011;

• 57th subject enrolled January 25, 2012;

• Primary tumour site = colorectal 9 (18%), breast 8 (16%), ovary 8 (16%), lung 5 (10%), others 20 (40%);

• Median number of previous treatments = 3.
CONSORT Diagram

56 Patients Approached
5 Declined
51 Patients Consented
1 Ineligible
50 Patients Enrolled

Patients Biopsied and Archival Specimens Collected

Pathological Processing
49 Biopsy Specimens
5 Insufficient Tumor

Pathological Processing
41 Archival Specimens
1 Insufficient Tumor

DNA Extraction
44 Biopsy Specimens
1 Insufficient DNA

DNA Extraction
40 Archival Specimens
0 Insufficient DNA

Molecular Analysis
43 Biopsy Specimens

Molecular Analysis
40 Archival Specimens

Mutation Genotyping
0 unsuccessful Genotyping

Mutation Genotyping
0 unsuccessful Genotyping

Targeted Gene Sequencing
1 unsuccessful Sequencing

Targeted Gene Sequencing
3 unsuccessful Sequencing

Molecular Profiling Report
16 Mutations in 14 Patients Identified

Molecular Profiling Report
13 Mutations in 12 Patients Identified

Impact on Treatment Decision
6 Patients had Treatment Decisions Impacted on by Molecular Profiling
Results: Mutations identified

• Biopsy specimens (43 patients)
  o 16 mutations in 14 patients
    • 13 actionable mutations (1 non-Oncocarta - KIT)
      – 100% agreement between platforms
    • 3 novel mutations detected by sequencing
      – PDGFRA in colon ca
      – AKT1 in breast ca
      – EGFR in carcinoma unknown primary

• Archival specimens (41 patients)
  o 13 mutations in 12 patients
    • 10 actionable mutations (2 non-Oncocarta – KIT, KRAS)
      – 95% agreement between platforms
    • 3 novel mutations detected by sequencing
Results: Biopsy/Archival concordance

Together (49 patients: 34 both, 9 biopsy only, 6 archival only, 1 neither)

- 19 mutations in 16 patients:
  - 16 actionable mutations (2 non-Oncocarta – KIT, KRAS);
  - 3 novel mutations (undergoing functional studies).

- 30/34 (88%) patients demonstrated biopsy/archival concordance:
  - PIK3CA mutation lost and another gained in cervical ca;
  - KRAS mutation gained in colon ca;
  - RET mutation lost in medullary thyroid ca.
  - EGFR mutations (2) gained in a lung adenoca

- High level of concordance
  - Median 33 months between biopsy and archival specimens
Results: Impact on treatment

• 6 patients had treatment decisions impacted by molecular profiling:
  o PIK3CA mutation in colon ca (PI3K/MEK combo);
  o PIK3CA mutation in breast ca (PI3K/MEK combo);
  o AKT1 mutation (novel) in breast ca (everolimus + chemo);
  o KRAS mutation in ovarian ca (PI3K/MEK combo);
  o RET mutation in medullary thyroid ca (sorafenib);
  o EGFR mutation (novel) in CUP squamous histol (erlotinib).

• All received matched treatment;
• 3 patients had a RECIST partial response, 1 patient had a minor response classified stable disease.
Results versus Objectives

• Primary
  – Demonstrate feasibility and optimize processes and procedures for collection and analyses of biopsies from cancer patients

<table>
<thead>
<tr>
<th>Feasibility defined as:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment:  ≥50% ✓ (89%)</td>
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<td>Acceptable biopsies: ≥90% ✗ (87%)</td>
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<td>Successful analysis: ≥90% ✓ (96%)</td>
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<td>Timeline &lt;3 weeks: ≥90% ✗ (57%)</td>
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<td>Actionable mutations: ≥30% ✓ (32%)</td>
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Other Comments

• Expert panel is crucial;
• Ideal to have CLIA-certified NGS to improve timeliness;
• FFPE is adequate, but problems associated with archived samples exists;
• Clinical benefit from profiling is dependent upon:
  o Identified mutations being actionable or potentially actionable;
  o Clinician being aware of mutation significance;
  o Matched treatment being available;
  o Patient being suitable for matched treatment.
• As gene list expands – increased heterogeneity is likely to be observed, but will it occur in driver mutations?

• Personalized cancer medicine… more work to do…
Clinical Genomics Study (1500 patients/4 yrs)

- Targeted cancer genes; expanded gene list and up to full exomes as appropriate
- Nested clinical trials of targeted drugs to assess patient benefit
- OICR Cancer Genomics Group will evaluate emerging technologies and methods
- CAP/CLIA/OLA facility verifying actionable variants identified in the research setting.
- Validation of NGS platforms in CAP/CLIA/OLA facility
- Bioinformatics and information tools
- GE3LS to assess socio-economics, preferences, KT
Dancey et al, Cell 2012
The Genetic Basis for Cancer Treatment Decisions

Janet E. Dancey, Philippe L. Bedard, Nicole Onetto, and Thomas J. Hudson.

Cancer Genomics: Technology, Discovery, and Translation

Ben Tran, Janet E. Dancey, Suzanne Kamel-Reid, John D. McPherson, Philippe L. Bedard, Andrew M.K. Brown, Tong Zhang, Patricia Shaw, Nicole Onetto, Lincoln Stem, Thomas J. Hudson, Benjamin G. Neel, and Lillian L. Stiu

See accompanying editorial on page 584
Cancer Genome Assessment Trial (CGAT)

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Management Core

Janet Dancey
Teresa Petrocelli
Thomas Hudson
ARCTIC Sponsors since 2004