Enriching TCGA with Patient Information: Potential Uses and Obstacles

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Type I versus Type II Endometrial Cancer

**Present Paradigm**

**Type I tumors**
- Comprise the majority of endometrial cancer
- Mostly endometrial adenocarcinomas
- Associated with unopposed estrogen stimulation
- Often preceded by hyperplasia

**Type II tumors**
- Predominantly serous and clear cell carcinomas
- Less well-differentiated
- Commonly estrogen ‘independent’
- Often arise in atrophic endometrium and derive from intraepithelial carcinoma
- ~40% of deaths but only 10-20% of tumors

Sherman ME, Mod Pathol 2000;13:295-308
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### New E2C2 Results

- Risk factor patterns for high-grade endometrioid tumors and type II tumors were similar
- Parity, oral contraceptive use, cigarette smoking, age at menarche, and diabetes were associated with type I and type II tumors to a similar extent
- Body mass index had a somewhat greater effect on type I tumors than on type II tumors
- Etiology of type II tumors may not be completely estrogen independent

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Sherman ME, Mod Pathol 2000;13:295-308

Challenge

Develop a comprehensive catalogue of endometrial cancer genes to guide prevention and therapeutic development
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- Only a handful of cancer genes are mutated at a high frequency; most cancer genes are mutated at an intermediate frequency (2-20%)
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- Characterizing the role of endogenous and exogenous factors in shaping the mutational landscape of endometrial cancer requires large numbers of well-annotated specimens
No. Samples Needed to Detect Significantly Mutated Genes as a Function of Median Background Mutation Frequency and Mutation Rate of Cancer Gene

Most of the significant gene \times tumor type pairs involve only a small fraction of patients

- One half of the significant pairs involved \leq 6.1\% of patients
- One quarter of the significant pairs involved \leq 3.1\% of patients

Current TCGA sample is inadequate to reliably detect genes mutated at <5\% above background

M Lawrence et al. Nature 2014;505:495-501
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- The best combination therapy for each endometrial cancer patient must be based on cellular pathways disrupted in her tumor and the nature of the specific disruptions
Mortality among Patients with Colorectal Cancer, According to Regular Use or Nonuse of Aspirin after Diagnosis and \textit{PIK3CA} Mutation Status

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{A Colorectal Cancer–Specific Mortality, Mutant \textit{PIK3CA} \hspace{1cm} B Colorectal Cancer–Specific Mortality, Wild-Type \textit{PIK3CA} \hspace{1cm} C Overall Mortality, Mutant \textit{PIK3CA} \hspace{1cm} D Overall Mortality, Wild-Type \textit{PIK3CA}}
\end{figure}

\textit{Liao X et al. NEJM} 2012;367:1596-1606.
## Genetic Heterogeneity versus Environmental Heterogeneity

### Genetic Heterogeneity

- **Intratumoral heterogeneity** among the cells of one tumor
- **Intermetastatic heterogeneity** among different metastatic lesions of the same patient
- **Intrametastatic heterogeneity** among the cells of an individual metastasis
- **Interpatient heterogeneity** among the tumors of different patients

### Environmental heterogeneity

- Do different endogenous / exogenous exposures / insults lead to unique mutations that may affect tumor type and prognosis?
Understanding Endometrial Cancer Biology

Challenge

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- The best combination therapy for each endometrial cancer patient must be based on cellular pathways disrupted in her tumor and the nature of the specific disruptions

Solution

Identify and understand the pathway-level implications of mutated genes to guide prevention efforts and to provide therapeutic options
Number of Somatic Mutations in Representative Human Cancers

B Vogelstein et al. Science 2013;339:1546-1558
In common solid tumors, ~33-66 genes display subtle somatic mutations that would be expected to alter their protein products.
Certain tumors such as lung cancer and melanoma display many more nonsynonymous mutations than average, probably reflecting the involvement of potent mutagens.
Mutation Spectra across Endometrial Carcinomas

Lung Cancer
43% and 13% C:G→A:T transversions are found in smokers and never smokers respectively, suggesting that C:G→A:T transversion events in non-synonymous mutations are likely induced by carcinogens in smoke (Ding et al. Nature 2008;455:1069)
Tobacco Smoking Associated with Higher Mutation Rate in Lung Cancer Are Hotspot Mutations in POLE Smoking-Related in Endometrial Cancer?

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**Endometrial Cancer**

~80% of the mutation events from mutations in POLE, a catalytic subunit of DNA polymerase epsilon that is involved in DNA replication and repair

Ultramutated tumors have a distinctive mutation spectrum, exemplified by an elevated frequency of C→A transversions similar to lung cancer among smokers

Number of Somatic Mutations in Representative Human Cancers

Tumors with mismatch repair defects can harbor thousands of mutations.

B Vogelstein et al. Science 2013;339:1546-1558
Pediatric tumors and leukemias harbor far fewer mutations < 10/tumor.

Number of Somatic Mutations in Representative Human Cancers

- Uterine endometrioid tumors: average ~ 62 mutations versus serous tumors ~ 29 mutations

B Vogelstein et al. Science 2013;339:1546-1558
138 Driver Genes Discovered to Date

<table>
<thead>
<tr>
<th>125 Driver Genes affected by Subtle Mutations + 13 Driver Genes affected by Amplification or Deletion</th>
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<tbody>
<tr>
<td>ABL1</td>
</tr>
<tr>
<td>ACVR1B</td>
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<tr>
<td>AKT1</td>
</tr>
<tr>
<td>ALK</td>
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<tr>
<td>APC</td>
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<tr>
<td>AR</td>
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<td>ARID1A</td>
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<tr>
<td>ARID1B</td>
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<td>ARID2</td>
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<td>ASXL1</td>
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<td>ATM</td>
</tr>
<tr>
<td>ATRX</td>
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<tr>
<td>AXIN1</td>
</tr>
<tr>
<td>B2M</td>
</tr>
<tr>
<td>BAP1</td>
</tr>
<tr>
<td>BCL2</td>
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</tbody>
</table>

>20% of recorded mutations in the gene are at recurrent positions and missense (54 oncogenes) or >20% of mutations are inactivating (71 tumor suppressor genes)

B Vogelstein et al. Science 2013;339:1546-1558
Discovery and Saturation Analysis of Cancer Genes Across 21 Tumor Types

Analysis of somatic point mutations in exome sequences from 4,472 human cancers

M Lawrence et al. Nature 2014;505:495-501
### Candidate Cancer Genes across 21 Tumor Types

#### 125 Driver Genes affected by Subtle Mutations + 13 Driver Genes affected by Amplification or Deletion

<table>
<thead>
<tr>
<th>Genes Affected by Subtle Mutations</th>
<th>Genes Affected by Amplification or Deletion</th>
</tr>
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<tbody>
<tr>
<td>ABL1</td>
<td>CCND1</td>
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<td>ACVR1B</td>
<td>CDKN2C</td>
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<tr>
<td>AKT1</td>
<td>IKZF1</td>
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<td>ALK</td>
<td>LMO1</td>
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<td>APC</td>
<td>MAP2K4</td>
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<tr>
<td>AR</td>
<td>MDM2</td>
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<td>ARID1A</td>
<td>MYEL1</td>
</tr>
<tr>
<td>ARID1B</td>
<td>MYCN</td>
</tr>
<tr>
<td>ARID2</td>
<td>NCOA3</td>
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<td>ASXL1</td>
<td>NFKB1</td>
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<td>ATM</td>
<td>TBX1</td>
</tr>
<tr>
<td>ATRX</td>
<td>TSC1</td>
</tr>
<tr>
<td>AXIN1</td>
<td>TTP</td>
</tr>
<tr>
<td>B2M</td>
<td>U2AF1</td>
</tr>
<tr>
<td>BAP1</td>
<td>VHL</td>
</tr>
<tr>
<td>BCL2</td>
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<td>BCL3</td>
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<td>BCL14</td>
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<td>BCL15</td>
<td></td>
</tr>
<tr>
<td>BCL16</td>
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</tr>
</tbody>
</table>

**Significant in 4+ tumor types**: ABL1, ACVR1B, AKT1, ALK, APC, AR, ARID1A, ARID1B, ARID2, ASXL1, ATM, ATRX, AXIN1, B2M, BAP1, BCL2, BCL3, BCL6, BCL10, BCL11, BCL12, BCL13, BCL14, BCL15, BCL16

**Significant in 3 tumor types**: ARID1A, ARID1B, ARID2, ATM, ATRX

**CTCF, ERBB3, HLA-A were significant in 3 tumor types but were missing from the Vogelstein list**: ARID2, ATM, BCL12

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M Lawrence et al. Nature 2014;505:495-501
Candidate Cancer Genes in TCGA Endometrial Cancer Specimens

<table>
<thead>
<tr>
<th>Gene</th>
<th>Long Name</th>
<th>Q-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN</td>
<td>phosphatase and tensin homolog (mutated in multiple advanced cancers 1)</td>
<td>3.40E-13</td>
</tr>
<tr>
<td>TP53</td>
<td>tumor protein p53</td>
<td>3.40E-13</td>
</tr>
<tr>
<td>KRAS</td>
<td>v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog</td>
<td>3.40E-13</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>phosphoinositide-3-kinase, catalytic, alpha polypeptide</td>
<td>3.40E-13</td>
</tr>
<tr>
<td>PIK3R1</td>
<td>phosphoinositide-3-kinase, regulatory subunit 1 (alpha)</td>
<td>3.40E-13</td>
</tr>
<tr>
<td>FBXW7</td>
<td>F-box and WD repeat domain containing 7</td>
<td>3.40E-13</td>
</tr>
<tr>
<td>CTCF</td>
<td>CCCTC-binding factor (zinc finger protein)</td>
<td>5.83E-13</td>
</tr>
<tr>
<td>ARID1A</td>
<td>AT rich interactive domain 1A (SWI-like)</td>
<td>8.17E-12</td>
</tr>
<tr>
<td>ARHGAP35</td>
<td>glucocorticoid receptor DNA binding factor 1</td>
<td>1.09E-08</td>
</tr>
<tr>
<td>FGFR2</td>
<td>fibroblast growth factor receptor 2 (bacteria-expressed kinase)</td>
<td>1.93E-06</td>
</tr>
<tr>
<td>ZFHX3</td>
<td>zinc finger homeobox 3</td>
<td>1.93E-06</td>
</tr>
<tr>
<td>PPP2R1A</td>
<td>protein phosphatase 2 (formerly 2A), regulatory subunit A , alpha isoform</td>
<td>7.09E-05</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>catenin (cadherin-associated protein), beta 1, 88kDa</td>
<td>1.28E-03</td>
</tr>
<tr>
<td>BCOR</td>
<td>BCL6 co-repressor</td>
<td>1.32E-03</td>
</tr>
<tr>
<td>CUX1</td>
<td>cut-like homeobox 1</td>
<td>3.74E-03</td>
</tr>
<tr>
<td>FAT1</td>
<td>FAT tumor suppressor homolog 1 (Drosophila)</td>
<td>6.17E-03</td>
</tr>
<tr>
<td>ARID5B</td>
<td>AT rich interactive domain 5B (MRF1-like)</td>
<td>6.68E-03</td>
</tr>
<tr>
<td>POLE</td>
<td>polymerase (DNA directed), epsilon</td>
<td>3.31E-02</td>
</tr>
<tr>
<td>CHD4</td>
<td>chromodomain helicase DNA binding protein 4</td>
<td>4.10E-02</td>
</tr>
<tr>
<td>SACS</td>
<td>spastic ataxia of Charlevoix-Saguenay (sacsin)</td>
<td>6.05E-02</td>
</tr>
<tr>
<td>ANK3</td>
<td>ankyrin 3, node of Ranvier (ankyrin G)</td>
<td>6.05E-02</td>
</tr>
</tbody>
</table>

M Lawrence et al. Nature 2014;505:495-501
Targeting the PI3K/AKT/mTOR Pathway in the Treatment of Endometrial Cancer

Variety of phase 1 and 2 trials underway with targeted agents

Slomovitz et al, Clin Cancer Res 2012;18:5856
Co-Factors in the PI3K/AKT/mTOR Pathway

Important to consider how co-factors such as hormone use, diabetes, and smoking influence response to targeted therapy.
In endometrial cancer there appears to be more than one mutation cluster: the largest patient cluster has a frequency of 1.5 mutations x 10^-6 / Mb, and a second cluster with a frequency 150x greater.

Multiple clusters suggest that factors other than age contribute to endometrial cancer.

High mutation frequencies association with DNA repair pathways: TP53, POLE.

Sequence context analysis found that endometrial cancers have a high proportion of guanine 1 base downstream of C>T transitions.

The C>T mutation at CpG is consistent with findings of aberrant DNA methylation in endometrial cancer.

Do Epigenetic Alterations and Chromatin Remodeling have a Critical Role in Endometrial Cancer?

**ARID1A**

- Encodes protein involved in chromatin remodeling complex (SWI/SNF) which regulates processes that require alteration of chromatin structure, including DNA repair, DNA synthesis, mitosis and genomic instability.

- Mutations in ARID1A gene associated with ~30% of both low- and high-grade endometrioid endometrial cancers, but not serous endometrial carcinomas.
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Loss of ARID1A expression associated with microsatellite instability

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ARID1A appears to be a causative gene instead of a target gene of MSI through epigenetic silencing of the MLH1 gene in endometrial carcinoma

Only ARID1A Associated with Survival in Endometrial Cancer TCGA

Understanding the role of ARID1A in the pathogenesis of endometrium-derived tumors is fundamental for future translational studies aimed at designing new diagnostic tests for early detection and identifying critical molecular targets for new therapeutic interventions.

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**CTCF**
- Candidate tumor suppressor for endometrial cancer
- Encoded protein can bind a histone acetyltransferase (HAT)-containing complex and function as a transcriptional activator or bind a histone deacetylase (HDAC)-containing complex and function as a transcriptional repressor
- Appears to be MSI target gene (Zighelboim… Goodfellow, Hum Mutat 35:63–65, 2014)

**ARID1A** appears to be a causative gene instead of a target gene of MSI through epigenetic silencing of the *MLH1* gene in endometrial carcinoma

**Loss of ARID1A expression associated with microsatellite instability**
- Microsatellite stable (MSS)
- Microsatellite instable ( MSI)

**Loss of ARID1A expression associated with sporadic MSI, not with MSI due to germline mutations**
- ARID1A wildtype
- ARID1A loss of expression

*T Bosse, et al. Mod Path 2013;26:1525-35*
Do Genistein and other Phytoestrogens Regulate Gene Activity by Modulating Epigenetic Events?

- The charts show the relationship between Total Isoflavones and Genistein, and their effect on gene activity (RR, 95% CI).

- Laboratory studies suggest that genistein and other soy-related isoflavones can reverse hypermethylation and reactivate silenced genes in breast cancer cell lines.

- In vitro data show that genistein can have a dose-dependent inhibition of DNMTA and HDAC activities, and increase active chromatin modifications near the transcription start site.

- NJ Ollberding et al. JNCI 2012;104:67-76
### Mutated Genes Associated with Endometriod versus Serous Histological Type in 230 Cases

<table>
<thead>
<tr>
<th>Gene</th>
<th>P-Value</th>
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<tr>
<td>TP53</td>
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<td>PIK3R1</td>
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<td>ARID1A</td>
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<td>CTCF</td>
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### Mutated Genes Associated with Age at First Birth in 230 Cases

<table>
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<td>PPP2R1A</td>
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## Tumor Stage, Histology, Grade, and Treatment for Endometrial Cancer Patients in TCGA

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<th></th>
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<td>Grade 3</td>
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<td>I</td>
<td>78 (89)</td>
<td>83 (79)</td>
<td>70 (63)</td>
<td>6 (46)</td>
<td>17 (32)</td>
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<td>3 (3)</td>
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<td>6 (5)</td>
<td>2 (15)</td>
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<td>25 (7)</td>
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<td>26 (23)</td>
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<td>4 (31)</td>
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<td>88 (100)</td>
<td>105 (100)</td>
<td>111 (100)</td>
<td>13 (100)</td>
<td>53 (100)</td>
<td>370 (100)</td>
</tr>
</tbody>
</table>

Lack of treatment information an impediment to the analysis of survival in the TCGA

Potential Research Questions

• Do tobacco smoking, BMI, pregnancy, exogenous hormones, age at menarche, race or other endometrial cancer risk factors affect endometrial cancer genomic profiles?
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• Do any of these factors moderate biological pathways that are activated / repressed during carcinogenesis?
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- Do any epi exposures influence tumor recurrence and potentially confound the genomic alteration-tumor recurrence associations?
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• Do any epi exposures influence tumor recurrence and potentially confound the genomic alteration-tumor recurrence associations?

• Do BMI, tobacco smoking or and / other or other factors influence methylation or chromatin remodeling of specific genes? Does this vary by grade or histologic type?
Summary

- Majority of TCGA samples have distinct alterations not shared by other specimens
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• Rare somatic mutations can be implicated as drivers (oncogenic contributors) by aggregating across tumor types

• Present challenge to determine whether rare aberrations are drivers or passengers (clonally propagated with neutral effect) and whether they are clinically actionable
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• Rare somatic mutations can be implicated as drivers (oncogenic contributors) by aggregating across tumor types

• Present challenge to determine whether rare aberrations are drivers or passengers (clonally propagated with neutral effect) and whether they are clinically actionable

• Hotspot mutations in DNA segments that encode particular protein domains may lead to the identification translational opportunities and new drug targets
Summary

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- Hotspot mutations in DNA segments that encode particular protein domains may lead to the identification translational opportunities and new drug targets

- Larger sample sizes in FFPE are needed that will allow researchers to identify important low-frequency mutations and GxE interactions
Author Contributions
The TCGA Research Network contributed collectively to this study. Biospecimens were provided by the tissue source sites and processed by the biospecimen core resource. Data generation and analyses were performed by the genome sequencing centers, cancer genome characterization centers and genome data analysis centers. All data were released through the data coordinating center. The National Cancer Institute and National Human Genome Research Institute project teams coordinated project activities

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Uterine serous carcinomas share many similar characteristics with basal-like breast cancer and serous ovarian cancer.

Compelling similarities between subsets of these cancers suggest that genomic-based classification may lead to improved management of these patients.

Clinicians should carefully consider treating copy number altered endometrioid patients with chemotherapy rather than adjuvant radiotherapy.

Clinical trials are warranted to identify translational opportunities for targeted therapeutics.

Corpus and Uterus
5-Year Relative Survival by Diagnosis Year, SEER, 1975-2005
Corpus and Uterus

Cell Fate
Genetic alterations in cancer abrogate the balance between differentiation and division, favoring the latter

Cell Survival
Cancer cells that acquire a mutation that allows it to thrive under limiting nutrient concentrations will have a selective growth advantage

Genome Maintenance
Mutations in genes, such as TP53 and ATM, that control DNA damage confer a selective growth advantage to cancer cells

B Vogelstein et al. Science 2013;339:1546-1558
Variety of phase 1 and 2 trials underway with targeted agents, including TKI, RAF inhibitors, mTOR inhibitors.