GIST 101: Understanding Your Pathology Report

GSI Patient Summit Saturday 22 September 2012

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Faculty, Sarcoma Research Center
GIST Pathology: Lecture Overview

1. What happens to my tumor in pathology?

2. What information is in my pathology report?

3. Why is this information there?

4. What is the evidence that the information is useful?

5. What is new and exciting in GIST pathology?
What happens to my tumor in pathology?
Tumor sample is received from the OR and logged into computer.

Tumor is examined by a pathologist.
Tumor is sampled and placed in plastic cassettes for further processing.

Tumor is also given to cytogenetics, tumor bank, molecular diagnosis and electron microscopy when appropriate.
The tissue blocks are fixed in formalin and then loaded on a tissue processor overnight.
Tissue processing is done overnight and utilizes graded treatments of formalin, ethanol, xylene and paraffin.
Blocks are retrieved from the tissue processor.
The tissue fragments are embedded in a paraffin mold and cooled – the result being a tissue block.
The paraffin-embedded blocks are loaded and cut using a microtome.
Tissue paraffin ribbons are placed in a warm waterbath and the picked up on glass slides.
The unstained slides can be used for H&E, special stains, immuno-histochemistry, molecular studies, etc.
Most slides are H&E (hemotoxlin & eosin) stained, given coverslips, organized and delivered to the proper pathologist.
Additional unstained slides can be cut at a later time.
After final diagnosis, both slides and the paraffin blocks from which they are cut are cataloged and stored for future use.
What information is in my pathology report?
Protocol for the Examination of Specimens From Patients With Gastrointestinal Stromal Tumor (GIST)

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: June 2012

Procedures
• Biopsy
• Resection

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Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

GASTROINTESTINAL STROMAL TUMOR (GIST): Resection

Select a single response unless otherwise indicated.

Procedure
___ Excisional biopsy
___ Resection
   Specify type (eg, partial gastrectomy):
___ Metastasectomy
___ Other (specify): ____________________
___ Not specified

Tumor Site
Specify (if known): ______________________
___ Not specified

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see “Comment”)

Tumor Focality
___ Unifocal
___ Multifocal
   Specify number of tumors: _____
   Specify size of tumors: __________________

GIST Subtype
___ Spindle cell
___ Epithelioid
___ Mixed
___ Other (specify): ____________________
Mitotic Rate
Specify: ___ /50 HPF

Note: The required total count of mitoses is per 5 mm² on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm². Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm². If necessary please measure field of view to accurately determine actual number of fields required to be counted on individual microscopes to count 5 mm².

Necrosis
+ ___ Not identified
+ ___ Present
   + Extent: ___%
+ ___ Cannot be determined
Histologic Grade (Note B)
___ Gx: Grade cannot be assessed
___ G1: Low grade; mitotic rate ≤ 5/50 HPF
___ G2: High grade; mitotic rate > 5/50 HPF

Risk Assessment (Note C)
___ None
___ Very low risk
___ Low risk
___ Intermediate risk
___ High risk
___ Overly malignant/metastatic
___ Cannot be determined

Margins
___ Cannot be assessed
___ Negative for GIST
    Distance of tumor from closest margin: ___ mm or ___ cm
___ Margin(s) positive for GIST
    Specify margin(s): ______________

Pathologic Staging (pTNM) (Note G)

TNM Descriptors (required only if applicable) (select all that apply)
___ M (multiple)
___ R (recurrent)
___ Y (posttreatment)

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence for primary tumor
___ pT1: Tumor 2 cm or less
___ pT2: Tumor more than 2 cm but not more than 5 cm
___ pT3: Tumor more than 5 cm but not more than 10 cm
___ pT4: Tumor more than 10 cm in greatest dimension

Regional Lymph Nodes (pN) (Note D)
___ Not applicable
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis

Distant Metastasis (pM) (Note D)
___ Not applicable
___ pM1: Distant metastasis
    + Specify site(s), if known: ______________

Additional Pathologic Findings
+ Specify: ______________
Ancillary Studies (select all that apply) (Note E)

**Immunohistochemical Studies**
- __ KIT (CD117)
  - ___ Positive
  - ___ Negative
  - ___ Others (specify): ______________________
  - ___ Not performed

**Molecular Genetic Studies (eg, KIT or PDGFRA mutational analysis)**
- ___ Submitted for analysis; results pending
- ___ Performed, see separate report: ______________________
- ___ Perform
  - Specify method(s) and results: ______________________
  - ___ Not performed

**Preresection Treatment (select all that apply)**
- ___ No therapy
- ___ Previous biopsy or surgery
  - Specify: ______________________
- ___ Systemic therapy performed
  - Specify type: ______________________
- ___ Therapy performed, type not specified
- ___ Unknown

**+ Treatment Effect (Note F)**
+ Specify percentage of viable tumor: ___%
Getting the diagnosis right.
Case 1

Female, aged 40, with 25 cm mass involving the small bowel.
Case 2

Male, aged 38, with 10 mm polyp at 10 cm in rectum.
Case 3

Male, aged 37, with 13 cm gastric wall mass.
Case 4

Male, aged 36, with 17 cm gastric wall mass.
Case 5

Female, aged 29, with 10 cm gastric wall mass.
## Immunohistochemical Scheme

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>KIT</th>
<th>CD34</th>
<th>Ker</th>
<th>SMA</th>
<th>DES</th>
<th>S-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIST</td>
<td>+</td>
<td>+(70%)</td>
<td>-</td>
<td>+(40%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+(sar)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Melanoma</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Fibromatosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Immuno histochemical Profile of GISTs (Circa 1997 and prior)

CD34 +ve (70%)
SMA +ve (30-40%)
Desmin –ve
S-100 protein –ve
Keratin –ve

Courtesy of Brian Rubin, U. Washington
Gastrointestinal Stromal Tumor

- Arise from the interstitial cells of Cajal (ICC)
- ICC have a “pacemaker” function and are important in coordinating peristalsis

Hornick & Lazar. GSI website: Understanding Your Pathology Report for GIST
### Immunohistochemical Profile of GIST

<table>
<thead>
<tr>
<th>H&amp;E</th>
<th>CD117 (KIT)</th>
<th>CD34</th>
<th>Smooth muscle actin</th>
<th>S100 protein</th>
<th>Desmin</th>
<th>Pan-keratin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95%</td>
<td>70%</td>
<td>30%</td>
<td>5%</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

- **KIT (CD117) +ve (95%)**
- **CD34 +ve (70%)**
- **SMA +ve (30-40%)**
- **Desmin –ve**
- **S-100 protein –ve**
- **Keratin –ve**
The many faces of GIST.
Exon 11
V559_V560del
Exon 9
A502_Y503dup
Detection of SNV in KIT Exon 10, currently not covered by Sanger

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Position</th>
<th>Gene Symb</th>
<th>Ploidy</th>
<th>Ref</th>
<th>Variant</th>
<th>VarFreq</th>
<th>Coverage</th>
<th>RefCov</th>
<th>VarCov</th>
</tr>
</thead>
<tbody>
<tr>
<td>chr4</td>
<td>5559346</td>
<td>KIT</td>
<td>Het</td>
<td>A</td>
<td>C</td>
<td>83.42</td>
<td>1077</td>
<td>389</td>
<td>663</td>
</tr>
</tbody>
</table>

Confirmation by Sanger
ATG→CTG, M541L
KIT EXON 10

75% Tumor
KIT immunoreactivity in GIST
Gastric GISTs with Distinctive Histology (Multinodular/Plexiform)

- Pediatric GISTs
  - Female predominance (peak 2nd decade)
  - Indolent, but late metastases common
  - Molecular genetic basis unknown

- Carney Triad
  - Gastric GIST, pulmonary chondroma, paraganglioma
  - Molecular genetic basis unknown

- Carney-Stratakis Syndrome
  - Gastric GIST and paraganglioma
  - Germline mutations in succinate dehydrogenase subunit genes (SDHA, SDHB, SDHC, or SDHD)
GIST with Distinctive Histology

- Multinodular/plexiform growth pattern
- Epithelioid or mixed morphology
- "Pediatric-type" or "type 2" GISTs
- Loss of SDHB staining by IHC
- Lymph node metastases common
- Distant metastases common – clinically indolent
- Current risk assessment criteria do not reliably predict behavior
- No response to imatinib
Pediatric-type GIST in an Adult

49-year-old female

Courtesy of Jason Hornick, BWH/Harvard, Boston, MA
Metastatic pediatric-type GIST
SDHB

“Wild-type” gastric GIST
Risk assessment in GIST
GIST – Prognostic Factors

- **Size**
- **Mitotic Rate**
- **Anatomic Location**
  - Pleomorphism
  - Cellularity
  - Necrosis
- **Mucosal Invasion**
- Proliferation Markers (Ki-67, Mib-1, PCNA, etc)
- DNA Flow Cytometry
- Image Analysis
- Nuclear Organizer Regions

**Problem** – Small GISTs without mitoses can metastasize!
NIH Consensus Risk Assessment

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Size</th>
<th>Mitotic Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low Risk</td>
<td>&lt; 2 cm</td>
<td>&lt; 5/50 HPF</td>
</tr>
<tr>
<td>Low Risk</td>
<td>2-5 cm</td>
<td>&lt; 5/50 HPF</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>&lt; 5 cm</td>
<td>6-10/50 HPF</td>
</tr>
<tr>
<td></td>
<td>5-10 cm</td>
<td>&lt; 5/50 HPF</td>
</tr>
<tr>
<td>High Risk</td>
<td>&gt; 5 cm</td>
<td>&gt; 5/50 HPF</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>Any Mitotic Rate</td>
</tr>
<tr>
<td></td>
<td>Any Size</td>
<td>&gt; 10/50 HPF</td>
</tr>
</tbody>
</table>

Fletcher et al., Hum Pathol, 2002
GIST: Sites of Involvement

- Rectum (5%)
- Esophagus (2%)
- Other (colon, mesentery, retroperitoneum)
- Stomach (25%)
- Small intestine (8%)

Omentum, mesentery, pelvis and retroperitoneum = EGIST (<1%)

Hornick & Lazar. GSI website: Understanding Your Pathology Report for GIST.
# 2007/2010 NCCN GIST Risk Assessment Guidelines***

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Parameters</th>
<th>Size</th>
<th>Risk of Progressive</th>
<th>Disease# (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gastric</td>
</tr>
<tr>
<td>Mitotic</td>
<td>≤ 2 cm</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
</tr>
<tr>
<td>Index</td>
<td>&gt; 2 ≤ 5 cm</td>
<td>Very low (1.9%)</td>
<td>Low (8.3%)</td>
<td>Low (4.3%)</td>
</tr>
<tr>
<td>≤ 5 per 50 hpf</td>
<td>&gt; 5 ≤ 10 cm</td>
<td>Low (3.6%)</td>
<td>(Insuff. data)</td>
<td>Moderate (24%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>Moderate (10%)</td>
<td>High (34%)</td>
<td>High (52%)</td>
</tr>
<tr>
<td>Mitotic</td>
<td>≤ 2 cm</td>
<td>None*</td>
<td>(Insuff. data)</td>
<td>High*</td>
</tr>
<tr>
<td>Index</td>
<td>&gt; 2 ≤ 5 cm</td>
<td>Moderate (16%)</td>
<td>High (50%)</td>
<td>High (73%)</td>
</tr>
<tr>
<td>&gt; 5 per 50 hpf</td>
<td>&gt; 5 ≤ 10 cm</td>
<td>High (55%)</td>
<td>(Insuff. data)</td>
<td>High (85%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>High (86%)</td>
<td>High (86%)</td>
<td>High (90%)</td>
</tr>
</tbody>
</table>

***Modified from Miettinen & Lasota, *Semin Diagn Pathol*, 2006 by Dr. Chris Corless, OHSU
Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GIST

Miettinen et al. 2005 and 2006
GIST - Gross Appearance
### 2007/2010 NCCN GIST Risk Assessment Guidelines***

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Parameters</th>
<th>Risk of Progressive Disease# (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Size</td>
<td>Gastric</td>
</tr>
<tr>
<td></td>
<td>≤ 2 cm</td>
<td>None (0%)</td>
</tr>
<tr>
<td></td>
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<td>Very low (1.9%)</td>
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<tr>
<td></td>
<td>≤ 5 per 50 hpf</td>
<td>&gt; 5 ≤ 10 cm</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>Moderate (10%)</td>
</tr>
<tr>
<td></td>
<td>Mitotic</td>
<td>None* (Insuff. data)</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 ≤ 5 cm</td>
<td>Moderate (16%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 per 50 hpf</td>
<td>&gt; 5 ≤ 10 cm</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>High (86%)</td>
</tr>
</tbody>
</table>

***Modified from Miettinen & Lasota, *Semin Diagn Pathol*, 2006 by Dr. Chris Corless, OHSU Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GIST
GIST - Recurrence-Free Survival Following Surgical Treatment of Primary GIST

- Recurrence-free survival is predicted by tumor size and mitotic index


![Graphs showing recurrence-free survival](https://via.placeholder.com/150)
FNCLCC Grading

- All three numbers are summated to determine degree of differentiation

Grade 1 : 2-3
Grade 2 : 4-5
Grade 3 : 6-8

- Proven to correlated well with survival

- **Mitotic Count.** In the most mitotically active area, ten successive high-power fields (at 400x magnification=0.1734 mm²) using a 40x objective.
  1. 0-9 mitoses per 10 HPFs
  2. 10-19 mitoses per 10 HPFs
  3. >20 mitoses per 10 HPFs

- **Tumor necrosis.** Evaluated on gross examination and validated with histological sections
  0. No tumor necrosis
  1. <50% tumor necrosis
  2. >50% tumor necrosis

- **Degree of Differentiation.** 1-3
GIST - Overall Survival by Risk Group

Risk Groups
- Normal pop.
- Very low
- Low
- Intermediate
- High
- Overtly malignant

Estimated proportion surviving

Years since diagnosis

Kindblom. at: http://www.asco.org
Clinical Characteristics of GIST

Wide age range – peak in 5\textsuperscript{th}-7\textsuperscript{th} decade

M = F

Small lesions = “incidentalomas”

Presenting symptoms include:
- abdominal pain,
- gastrointestinal bleeding,
- early satiety,
- symptoms referable to a mass
Treatment can cause big changes.
Treatment effect

Pre-Imatinib

Post-Imatinib (8 weeks therapy)
Case No. 22 - Marked Effect – 7 days pre-op (exon 11)
Case No. 12 - Marked Effect – 5 days pre-op (exon 11)
Case 8. - Moderate Effect – 3 days pre-op (exon 11)
Case 11. - Moderate Effect – 5 days pre-op (exon 11)
Case 20. Minimal Effect – 5 days pre-op (exon 11)
Results

- **Minimal effect:** 11/25 (44%)
- **Moderate effect:** 10/25 (40%)
- **Marked effect:** 4/25 (16%)
- No moderate or marked changes seen in control cases (p<0.0009)
Minimal and Moderate effects were seen across all durations of therapy

- Marked effect appeared to be a late finding peaking at 5 days
Long term Imatinib Tx
Long term Imatinib Tx
What is new and exciting in GIST pathology?
Chromosomal complexity and prognosis

97 chromosomes and more than 50 translocations
Chromosomal complexity in sarcomas

- Alain Aurias and Frédéric Chibon
- Sarcomas with a complex genetic profile
- Array-CGH and expression profile analyses
- Which genes / pathways are related to the chromosomal complexity?
- Is there a link between chromosomal complexity and prognosis?

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
Chromosomal instability signature
Carter et al Nat Genet 2002

• Computational method for evaluating aneuploidy
• Analysis of genes differentially expressed according to the level of aneuploidy
• Aneuploidy is a consequence of chromosomal instability (CIN)
• CIN70 signature predicts survival in several types of cancers
• No prediction in our series of sarcomas

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
CINSARC: arrayCGH analysis and correlation with FNCLCC grading

« Arm » Profile

« Rearranged » Profile

p = .001

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
Genomic complexity and prognosis
Possible approaches

• (Histological grading)
• Array-CGH
• Carter signature
Molecular grading in sarcomas

3 t tests to compare the expression profiles of tumors classified according to:

- CGH: 86 genes
- Grade: 73 genes
- Carter: 39 genes

GO analysis:
To identify the underlying pathways
Selection of genes involved in the most significantly overrepresented pathways (p<10^{-5})

- 37 genes
- 18 genes
- 39 genes

67 genes

Complexity INdex
In SARComas
CINSARC

Chibon et al, Nat Med 2010; 16: 781-7
CINSARC is a signature related to chromosome management and mitosis control associated with genome complexity.
CINSARC: Prognostic signature?

Prognostic value of CINSARC:
Metastasis free survival

Cohort 1

Cohort 2

CINSARC is an independent prognostic factor

Multivariate analysis

HR = 3.1; 95% CI [1.8 – 5.4]

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresc Sarcoma Group)
CINSARC and GIST

In-silico study of 32 GISTs
(Yamaguchi et al 2008)

n=32
p=0.003

Metastasis free survival

n=16

n=32  p=0.003

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>10</th>
<th>14</th>
<th>15</th>
<th>22</th>
</tr>
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<tbody>
<tr>
<td>GIS 1:</td>
<td>-1p distal, -22q</td>
<td></td>
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<tr>
<td>GIS 2:</td>
<td>-1p distal, -22q, -14q</td>
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<td>GIS 3:</td>
<td>-1p, -22q, -14q, -15q</td>
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<td>GIS 4:</td>
<td>-1p, -22q, -14q, -15q, -10</td>
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</table>
GIST and molecular signature

- 67 patients (Leuven + Bordeaux)
- Localised GIST
- No adjuvant treatment
- Frozen tissue from primary
- Miettinen classification
- Follow-up

CINSARC

Disease Free Survival

p log rank = 5.44e-09

C1: 35 cases
C2: 29 cases

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
GIST and molecular signature


AURKA is a prognostic factor in GIST

Bergonié + Leuven

Yamagushi et al JCO 2008

n = 32
p = 9.5 x 10^-4
AURKA – top ranked gene in CINSARC

- Gene maps to chromosome 20q13
- Mitotic centrosomal protein kinase
- Control of chromosome segregation
- Overexpression induces centrosome duplication/distribution abnormalities and aneuploidy
- Overexpression associated with poor prognosis in several cancers

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
Prognosis in GIST

- *AURKA* is overexpressed in aggressive GIST
- No amplification of *AURKA*
- Deletion of p16 (*CDKN2A*) or *RB1*
- Likely causal events leading to increase *AURKA* and CINSARC gene expression, chromosomal instability and complexity, and finally to metastasis
Genomic Index (GI) is a prognostic factor in GIST...

GI = Alt² / nb of altered chr.

• Frozen tissue is rarely available
• Method applicable on paraffin tissue?
• Genomic Index (GI) on CGH

n = 66
p = 8.9 x 10⁻¹⁰

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
**GIST and molecular signature**


Miettinen classification

CGH-Genomic Index

Frozen Tissue

FFPE bloc

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
Intermediate GIST and array-CGH

81 intermediate-risk (AFIP) GISTS
Array CGH from FFPE blocks

- Leuven (M Debiec-Rychter)
- Köln (E Wardelmann)
- Warsaw (P Rutkowski)
- Treviso (AP Dei Tos)
- French Sarcoma Group

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
Thank You

- Brian Rubin, Cleveland Clinic.
- Jason Hornick, Brigham & Women’s Hospital/ Harvard
- Jean-Michel Coindre & Frederic Chibon, Bordeaux, France (French Sarcoma Group)
- Michael Heinrich & Chris Corless, University of Oregon.
- Jon Trent, University of Miami.
- Colleagues at UTMDACC.