The Role of Diagnostic Management Teams in Improving Personalized Medicine and Reducing Provider Burden

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I have no conflicts of interest related to this presentation.
Objectives for Parts 1 and 2

• Learn about the Diagnostic Management Team (DMT)

• Understand the COVID-19 Diagnostic Management Team: Activity and Clinical Benefits

• Appreciate how the DMT can be moved forward and scaled across institutions and disease categories
Part 1

The Diagnostic Management Team:

How It Works and What It Does
The First Step in a Patient Encounter is Obtaining the Correct Diagnosis

Treating an Illness a Patient Does Not Have Hurts the Patient at an Enormous Cost to the Healthcare System
Wrong Diagnosis

Ineffective Treatment

- Improved Despite Incorrect Treatment
- Illness Progressed

Major Cause of Chronic Disease and Preventable Death
Why is Choosing the Correct Tests, and Only the Correct Tests, so Difficult?

• Personal and family history – Inaccuracies?
• Physical Examination: Fewer than 50 things to note
• Imaging Studies: Fewer than 50 tests
• Microscopic Evaluations: Fewer than 50 tests
• Clinical Laboratory Tests: Greater than 5000 tests with many genetic results
Four Major Conclusions of the National Academy of Medicine Report on Diagnostic Error in the US 2015

Diagnostic error is the major contributor to preventable death of all medical errors

Diagnosis should be a “team sport”

Diagnostic error has been poorly recognized for decades

No practitioner can be current about all topics without input of expert diagnosticians
What is the Diagnostic Management Team?

Making Diagnosis “A Team Sport” with Participation of Content Experts with Specialized Diagnostic Knowledge
Passive Clinical Laboratory: Most of the United States in 2022

Ordering Doctors

Diagnostic Doctors

Isolated Diagnostic Bits of Data - Assembly by Ordering Physician Minimally Trained in Test Selection and Interpretation
Diagnostic Management Team Approach

Ordering Doctors

Caring for More Patients While Diagnostic Puzzle is Being Assembled

Conferring Diagnostic Doctors

Isolated Diagnostic Bits of Data Being Merged with Clinical Data about the Patient by the Diagnostic Doctors

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Diagnostic Management Team Approach

Ordering Doctors

Solved Diagnostic Puzzle

Conferring Diagnostic Doctors

There Is No Wall between the Ordering Doctors and the Diagnostic Doctors

Receives Accurate Diagnosis Quickly as a Completed Puzzle
Instead of Providing Information that is a Set of Numbers, Difficult to Understand Abbreviations of Test Names, or Simple “Positive” or “Negative” Answers,

A Narrative Report Understandable to All Healthcare Providers is Delivered
Data Presentation in the Medical Record for Coagulation Studies Prior to Initiation of the Patient-specific, Expert-driven Coagulation Interpretations

JUNE 30, 2010

Pat-PT: 13.9   PT-inr: 1.1
PTT-pt: 43.6*   PoolNP: 8.1
P+N0Hr: 38.3   P+N1Hr: 6.2
P+N2Hr: 35.9   Pat-TT: 15
F8Act: 95     F9Act: 102
RVVT: 1.5*     DRVVT: Lupus
Anticoagulant Confirmed
DMX: 1.3     F11Act: 96     F12Act: 54
Report in the Medical Record

After Initiation of the Daily Rounds to Interpret All Complex Evaluations from the Special Coagulation Laboratory

With Test Selection Aided by a Current DMT Created Algorithm Entitled “Prolonged PTT Evaluation”
This patient has an elevated PTT, with a normal PT/INR and normal thrombin time.

A PTT mixing study failed to correct into the normal range.

These results are consistent with the presence of an inhibitor (such as a lupus anticoagulant) in the sample.

The Dilute Russell Viper Venom time (dRVVT) is used for detection of Lupus Anticoagulant, and the test was positive, indicating the presence of a Lupus Anticoagulant.
Conclusion

Taken together, this is a patient with a prolonged PTT based upon the presence of a lupus anticoagulant. There is no increased bleeding risk for the patient despite the prolonged PTT.
Goals of a DMT

Involve diagnostic experts with high-level content knowledge to:

• Optimize the selection of laboratory tests
• Shorten the time to diagnosis
• Increase the accuracy of diagnosis
# Active DMTs at UTMB

<table>
<thead>
<tr>
<th>Coagulation</th>
<th>Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicology</td>
<td>Blood Bank (RBC incompatibility)</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Questionable Child Abuse</td>
</tr>
</tbody>
</table>

**COVID-19**

**Two DMT’s Currently in Development**

Anemia and Pharmacogenomics
Selected Benefits of DMTs at UTMB

Coagulation – Shortens length of stay for patients with Bleeding and Clotting disorders

Toxicology – Identifies patients unresponsive to opioids for pain and patients who use opioids incorrectly

Autoimmunity – Identifies specific autoimmune disorders to improve treatment response
Selected Benefits of DMTs at UTMB

Liver Disease – Identifies early rejection of transplanted livers to permit retention of transplant

Blood Bank (RBC incompatibility) – Reduces the number and severity of RBC transfusion reactions

Questionable Child Abuse – Thus far, reunited more than 40 families and led to the release or dropped charges of more than 50 falsely convicted caregivers
Personalized Medicine – Every case is unique in some meaningful way

Consider the following 3 cases that are identical except for one attribute
PATIENT 1

This patient is a 26 year old woman with an enlarged left leg and shortness of breath. Her body mass index is 35 (obese). She was recently diagnosed with Type 2 diabetes.

Many tests are needed to evaluate the patient and make a diagnosis.
PATIENT 2
This patient is a 26 year old woman taking oral contraceptives with an enlarged left leg and shortness of breath. Her body mass index is 35 (obese). She was recently diagnosed with Type 2 diabetes.

Additional tests are needed to evaluate the patient and make a diagnosis.
PATIENT 3
This patient is a 26 year old woman with an enlarged left leg and shortness of breath and a family history of deep vein thrombosis. Her body mass index is 35 (obese). She was recently diagnosed with Type 2 diabetes.

Additional tests are needed to evaluate the patient and make a diagnosis.
The diagnostic puzzle for a diagnosis requires expertise in cases not considered complex by most doctors.

Consider a patient presenting with a blood clot in the leg – a deep vein thrombosis.

The puzzle has several sections to be completed by the diagnostic expert.
Evaluation for Presence and Location of Thrombosis and Cause for Thrombosis: Benefit if Coagulation DMT Involved

- Unilateral leg swelling
- US positive for DVT
- CAT of chest shows segmental PE
- Shortness of breath
- Mutation in Gene for Protein C
- Protein C activity 38%
- eGFR is 40
- Ddimer increased
Evaluating the Selection and Response to Anticoagulant Therapy:
Tremendous Benefit if Coagulation DMT Involved

Warfarin selected as anticoagulant with low eGFR

First INR value with 5 mg warfarin is 7.3

3 Repeat INR values with 5 mg warfarin all >5.0

Latest INR is 15 with minor bleeding

KCentra given with shortening of INR to normal

PGX shows CYP2C9 mutation to explain hyperresponse
Further Evaluation for Thrombotic Risk to Identify New “Second Hit” for Thrombosis: Tremendous Benefit if Coagulation DMT Involved

Nocturia for 3 years with multiple UTIs

PSA is 12.6

Imaging of prostate consistent with mass

Biopsy of mass indicates prostate cancer Gleason 7

Second hit for current thrombosis is malignancy

Prostatectomy can remove thrombotic risk factor

Prophylactic dosing of anticoagulant after prostatectomy
It is my opinion that:

The creation of lists and the use of complex diagnostic algorithms could reduce the diagnostic error rate if the information is placed in the hands of expert diagnostic doctors in a DMT.

The decision of the next step in the evaluation involves the selection among more than 10,000 tests.
Deep expertise in more than 50 disease groups – like > 20 types of cancer, anemia, and abnormal drug response to name a few – needs to be provided by individuals with very current knowledge about a selected group of diseases.
Part 2

The Implementation of the COVID-19 Specific Diagnostic Management Team with Clinical Impact
Personalized Interpretations of COVID-19-related Tests:

If There Was Ever a Case for a Diagnostic Management Team, This Is It
The Infrastructure of the DMT at UTMB is in Place

Clinical lab scientist generates results and gives them to a resident who provides a preliminary interpretation to the attending pathologist who reviews the case and enters it into the medical record
What Do Patient-facing Doctors Really Want to Know About a Patient Who May Have a COVID-19 Infection?

- Does this patient have, or has ever had, COVID-19?
- Can this patient join the family? Go to work?
- Does the patient have immunity to future COVID-19 infections?
What is the percentage of doctors who believe they can make accurate conclusions when PCR tests are falsely negative in approximately 33% of cases and when more than 150 poorly validated antibody tests have been approved prepared by the FDA?
Could most doctors “not know what they do not know” and transmit incorrect information to patients with significant consequences?
There are thousands of manuscripts published on the following topics:

- COVID-19-related PCR and related genetic tests
- Antibody tests for COVID-19
- Tests for SARS-CoV-2 variants
- Tests for Neutralizing antibodies
- Tests for T-cell immunity
These papers would have to be read and understood by the person creating the interpretation and associated recommendations.
We have created more than 140 combinations of test results that involve a PCR test, a test for IgG anti-COVID-19 antibodies, and a test for IgM anti-COVID-19 antibodies.

All of these paragraphs are continuously updated by the pathologist in charge of the DMT.
Major Academic Medical Centers Initially Avoided Antibody Tests Completely

(CNN) — Antibody tests used to determine if people have been infected in the past with Covid-19 might be wrong up to half the time, the US Centers for Disease Control and Prevention said in new guidance posted on its website.
A difficult, but absolutely critical job:

Identify the assays, validate them, and then provide an interpretation, without a request to do so, an expert-driven, patient-specific paragraph

How is this done for thousands of cases per day?
The Modified Infrastructure of the DMT at UTMB for the COVID DMT

Clinical lab scientist to Epic which presents a suggested interpretation of the COVID related test results to the resident to attending pathologist to the medical record
Good evening,

Attached is the list of COVID-19 DMT cases completed today. As of 5:55 PM, all code 900 cases have interpretations entered with the appropriate codes assigned. Additionally, one custom interpretation was created.

Thank you very much.

Best,
Alex
Comment Number Identified by Epic and Approved as Correct

**Code 78 → labeled as 905:**
1. 892913N
2. 140802P
3. 092506M
4. 063824Q
5. 423951Q
6. 338383N
7. 687201P

**Code 79:**
- 784309Q
- 587047P
- 389667P
- 270635P
- 577109P
- 669805Q
- 767691N
- 263338N

**Code 84:**
1. 395784Q
2. 787180N
3. 177772A
4. 421145P
5. 155167A
6. 894922P

**Code 85:**
1. 451222N
2. 144933A
3. 388677Q
4. 009107D
5. 892784N
6. 154403A
7. 807425P
8. 621296P
9. 311117N

**Code 86:**
1. 530056N

**Code 116:**
1. 137474A

**Code 121:**
1. 420193N

**Code 124:**
1. 074022Q

**Code 125:**
1. 850714N

**Code 126:**
1. 927055N
2. 679722N
3. 902982N
4. 391142P
5. 800637P
6. 134998P
7. 823531N
8. 465087N
9. 934438Q
10. 122083P
11. 595198N
Actual Case Example:

False Negative PCR with Positive IgM and COVID-19 Symptoms
Test Results and Clinical Picture

- PCR Negative on 3/1/21 and 3/4/21
- IgM Positive on 3/4/21; IgG negative on 3/4/21
- Symptoms since 2/28/21 with cough, shortness of breath, dry mouth, dizziness, fever, loss of appetite, chest pain, nausea, and fever; parents had COVID-19 and were recently discharged from the hospital
- Fever of 100.2 F in clinic on 3/1/21. O2 saturation as low as 88%
Description of Interpretive Report

First paragraph focuses on molecular tests and whether there is an active infection:

• Is there active infection?
• If test is negative, could it be a false negative?
• How to determine if the patient is recovered from an active infection?
• What to do if the patient is symptomatic?
Molecular NAAT Tests for Active Infection with the SARS-CoV-2 Virus:

The patient has currently tested negative twice consecutively (3/1/2021 and 3/4/2021) for the SARS-CoV-2 virus that causes COVID-19 illness. However, the patient has known COVID-19 positive contacts, has had symptoms consistent with COVID-19 illness, and has tested positive for SARS-CoV-2 IgM antibodies within a week of symptom onset. Therefore, these two recent negative tests are likely false negative tests, as the false negative rate using a nasopharyngeal sample can be up to 30% depending on the timing of sample collection in relation to illness onset and any deficiencies in sampling techniques.
In mild-to-moderate illness, the patient may be considered no longer infectious when it has been at least 10 days since symptom onset, the patient has been afebrile for 24 hours without the use of fever-reducing medications, AND other symptoms of COVID-19 are improving. However, in patients who have been severely ill with COVID-19 or are severely immunocompromised, isolation up to 20 days after symptom onset is recommended.
Second Paragraph Focuses on the Antibody Response

- IgM result and its association with prior infection status
- IgM result and timing of sample collection
- IgG result and its association with prior infection status
- IgG result and timing of sample collection
- Explanations related to immunity, duration of antibody response, and failure of some patients to mount antibody response
Tests for IgM and IgG Antibodies to the SARS-CoV-2 Virus:

The patient has tested positive for SARS-CoV-2 IgM antibodies and negative for SARS-CoV-2 IgG antibodies. Based on the patient’s clinical presentation, this is consistent with early-to-mid SARS-CoV-2 infection, as SARS-CoV-2 IgM antibodies are typically produced within 1-3 weeks from onset of infection and IgG antibodies typically become detectable within 2-3 weeks or more from the onset of infection.
Testing for antibodies approximately 3 weeks after illness onset will likely indicate whether the patient has produced IgG antibodies to the SARS-CoV-2 virus. However, some patients may take longer to develop detectable IgG antibodies, while some patients who were infected with SARS-CoV-2 may never develop IgG antibodies. While IgG antibodies to SARS-CoV-2 may provide some degree of immunity, at this time the strength and duration of the IgG antibody response is unknown. IgM antibodies, in contrast, typically decline by week 5 of illness onset and almost disappear by week 7.
The Outcome Question?

How Many Patients had an Improved Outcome?
## COVID-19 Cases and Outcomes at UTMB

<table>
<thead>
<tr>
<th>Hospital</th>
<th>COVID-19 Cases</th>
<th>% Cases w/ COVID-19</th>
<th>Mean LOS (Obs)</th>
<th>% ICU Cases</th>
<th>Mean ICU Days</th>
<th>% Early Deaths</th>
<th>% Deaths (Obs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTMB-Health</td>
<td>1,235</td>
<td>8.5</td>
<td>6.5</td>
<td>4.4</td>
<td>2.2</td>
<td>0.6</td>
<td>7.0</td>
</tr>
<tr>
<td>Mid Continental Region</td>
<td>34,510</td>
<td>7.5</td>
<td>8.3</td>
<td>22.6</td>
<td>9.8</td>
<td>1.0</td>
<td>10.1</td>
</tr>
<tr>
<td>AMCs</td>
<td>97,453</td>
<td>5.8</td>
<td>10.4</td>
<td>24.8</td>
<td>10.9</td>
<td>1.7</td>
<td>13.3</td>
</tr>
<tr>
<td>National</td>
<td>249,905</td>
<td>6.2</td>
<td>9.1</td>
<td>23.3</td>
<td>9.7</td>
<td>1.8</td>
<td>12.7</td>
</tr>
</tbody>
</table>

Similar Less Far Less

[utmb Health logo]
What is Different about UTMB?
Many Possible Variables

A Patient-specific, Expert-driven Comment on Infectious Status and Antibody Response is the Only Obvious One

Turnaround Time for In-lab High Sensitivity PCR Test Results Was Short at 0.5 to 1.5 Days
The Testing and Result Interpretation for COVID-19 Infection is Becoming More Complex Quickly: 

With a Greater Need for Diagnostic Accuracy 

There is a plan to initiate an Advanced COVID-19 DMT
A single viral particle with a mutation survives and grows. This one virus has a mutation-antibody to COVID-19 kills the rest.
The UK Variant: B.1.1.7

Many Mutations in the Gene for the Spike Protein
Mutations in the B.1.1.7 Lineage: Eight Mutations in Spike Gene

Spike Proteins in the B.1.1.7 Lineage Have Two Deletions and Six Substitutions in this Sequence of Amino Acids

At binding site to cell

- Asparagine (P+) \(\rightarrow\) Tyrosine (P-)
- Alanine (NP) \(\rightarrow\) Aspartate (-)
- Proline (NP) \(\rightarrow\) Histidine (+)
- Threonine (P-) \(\rightarrow\) Isoleucine (NP)
- Serine (P-) \(\rightarrow\) Alanine (NP)
- Aspartate (-) \(\rightarrow\) Histidine (+)

P: Polar; NP: Non-Polar; +: Pos; -: Neg

Mutation in the Area of the Receptor Binding Domain are a Major Focus of Concern

The U.K. variant

The South Africa variant
Omicron Variant

18 aa mutated residues in the Spike protein
8 residues in >60% of available sequences

43 aa mutated residues in the Spike protein
34 residues in >60% of available sequences

The structure of SARS-CoV-2 spike protein showing the active site in orange and the residues coloured against different mutational rate.
Coronavirus Variants Now Being Named by Letters of Greet Alphabet

<table>
<thead>
<tr>
<th>Given Name</th>
<th>Early Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>UK</td>
</tr>
<tr>
<td>Beta</td>
<td>South African</td>
</tr>
<tr>
<td>Gamma</td>
<td>Brazil</td>
</tr>
<tr>
<td>Delta</td>
<td>India</td>
</tr>
</tbody>
</table>
Coronavirus Variants Now Being Named by Letters of Greet Alphabet

<table>
<thead>
<tr>
<th>Given Name</th>
<th>Early Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epsilon</td>
<td>California US</td>
</tr>
<tr>
<td>Zeta</td>
<td>Brazil</td>
</tr>
<tr>
<td>Eta</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Theta</td>
<td>Philippines</td>
</tr>
</tbody>
</table>
## Coronavirus Variants Now Being Named by Letters of Greet Alphabet

<table>
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<tr>
<th>Given Name</th>
<th>Early Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iota</td>
<td>US</td>
</tr>
<tr>
<td>Kappa</td>
<td>India (1.617.1)</td>
</tr>
<tr>
<td>Lambda</td>
<td>Peru December 2020</td>
</tr>
<tr>
<td>Mu</td>
<td>Colombia</td>
</tr>
<tr>
<td>Omicron</td>
<td>South Africa</td>
</tr>
</tbody>
</table>
Variant Classification scheme defines three classes of SARS-CoV-2 variants:

- Variant of Interest
- Variant of Concern
- Variant of High Consequence
Even Improving the Outcome by One Level of Severity is a Major Victory for Vaccines

Prevention of Infection is the Main Goal BUT

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Asymptomatic</strong></td>
<td>![Star]</td>
</tr>
<tr>
<td><strong>No hospitalization</strong></td>
<td>![Star]</td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td>![Star]</td>
</tr>
<tr>
<td><strong>Intensive Care</strong></td>
<td>![Star]</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
</tr>
</tbody>
</table>

Commonly encountered in vaccinated patients
What will the Advanced COVID-19 DMT Consider?

Neutralizing Antibody

T Cell Immunity

Variant Analysis for All Cases Positive by PCR
From the first DMT in 1995 at the Massachusetts General Hospital

DMTs in Many Clinical Areas Have Been Developed

The DMT for COVID-19-related Tests Has Been Especially Valuable Clinically
How the DMT can be moved forward and scaled across institutions and disease categories
One Plan is to Create Regional, National or International Diagnostic Management Teams

Ideally, the Implementation of a Global DMT Service Could Be Provided by Experts Who are Paid for Their Services
Who Can Provide this Consultation on the Diagnosis?

Someone Who Knows the Correct Tests and the Diagnostic Parameters of the Tests in Use

Someone Who Can Expedite a Clinical Diagnostic Evaluation Because They Are In Charge of Diagnostic Testing in the Laboratory
What Cannot Work

One medical center with laboratory experts in dozens of clinical areas

No institution has a diagnostic expert for all diseases
What Will Surely Happen if Done Well

Dramatic Increases in the Number of Accurate Diagnoses Will Occur Within a Much Shorter Timeframe of the Patient’s Illness

Rapid and Accurate Diagnosis will Significantly Reduce the Number of Patients Who Would Otherwise Develop Painful and Expensive Chronic Disease
We Need to Contribute More Than Just a Test Result

We Need to Provide Information that Helps Patients Get a Rapid and Accurate Diagnosis with Only the Correct Tests
We Must be Ready for the Moment When Millions of Patients Realize that Their Complex Diagnosis Could Have Been Made with Less Suffering and Less Cost