Pre-MDS states: CHIP, CCUS, ICUS – How to manage in the clinic?

08 Dec 2023

MDS Foundation Breakfast Symposium
Annual American Society of Hematology Meeting, San Diego, CA

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Disclosures

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Chad Potts, MS

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Yu Wang, PhD

The Patients
The Families
The Mice

CHIVE TEAM
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fighting blood cancers

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Music’s Promise for Curing Cancer
Clonal Hematopoiesis of Indeterminate Potential (CHIP) is 3-6% at 60yo

While CH in small variant allele fractions are ubiquitous, the term of CHIP refers to clones present in a substantial number of cells (usually >2% VAF), and repeatedly occur in genes related to epigenetic function, splicing, and DNA damage repair.

“CHIP Genes” = Commonly mutated Genes in Myeloid Disease

• *Though incidence is different than what is seen in myeloid disease*

• Many of the genes are implicated in one of the following roles:
  1. Epigenetic regulation
  2. Splicing
  3. DNA damage response

DNMT3A-mutant monocytes display robust inflammatory signatures

Abplanalp et al., Circ. Res., 2021
Mutant TET2 boosts inflammatory signaling in primary monocytes

Heimlich et al., bioRxiv, 2022
Age associated CH and a model of malignant transformation
Risk of Transforming to MDS is...

1. Specific *Mutation* Dependent

Red – mutations in MN-like genes (SRSF2, SF3B1 etc), high allele burden, compound mutations

Blue – DTA mutations, lower allele fractions, and single mutations.

Galli et al, Blood, 2021; 138(11),965-976.
Risk of Transforming to MDS is...

2. VAF Dependent

Red – mutations in MN-like genes (SRSF2, SF3B1 etc), high allele burden, compound mutations

Blue – DTA mutations, lower allele fractions, and single mutations.
Risk of Transforming to MDS is...

3. Combination/Signature Dependent

Red – mutations in MN-like genes (SRSF2, SF3B1 etc), high allele burden, compound mutations

Blue – DTA mutations, lower allele fractions, and single mutations.

Galli et al, Blood, 2021; 138(11),965-976.
Risk of Transforming to MDS is...

4. Probably *variant* dependent

Red – mutations in MN-like genes (SRSF2, SF3B1 etc), high allele burden, compound mutations

Blue – DTA mutations, lower allele fractions, and single mutations.

Galli et al, Blood, 2021; 138(11),965-976.
Risk of Transforming to MDS is...

4. Probably *variant* dependent

815 DNMT3A R882H Exhibits Greater Inflammatory Potential Than R882C in Primary Hematopoietic Stem and Progenitor Cell Knock-in Model and Population Data

Program: Oral and Poster Abstracts
Type: Oral
Session: 503. Clonal Hematopoiesis, Aging and Inflammation: From Omics to Discoveries
Hematology Disease Topics & Pathways:
Research, Translational Research, CHIP, genomics, hematopoiesis, Biological Processes, Technology and Procedures, gene editing, Study Population, Human, omics technologies

Monday, December 11, 2023: 3:45 PM

Alexander Silver
MSTP Student
Vanderbilt SOM
Prediction of Risk for Myeloid Malignancy in Clonal Hematopoiesis

Lachelle D. Weeks, M.D., Ph.D.,1,2,3 Abhishek Niroula, Ph.D.,4,5 Donna Neuberg, Sc.D.,6 Waihay Wong, M.D., Ph.D.,7 R. Coleman Lindsley, M.D., Ph.D.,1,2 Marlise R. Luskin, M.D., M.S.C.E.,1,2 Nancy Berliner, M.D.,2,8 Richard M. Stone, M.D.,1,2 Daniel J. DeAngelo, M.D., Ph.D.,1,2 Robert J. Soiffer, M.D.,1,2,3 Md Mesbah Uddin, M.Sc., Ph.D.,9,10 Gabriel Griffin, M.D.,6,7 Caitlyn Vlasschaert, M.D., M.Sc.,11 Christopher J. Gibson, M.D.,1,2 Siddhartha Jaiswal, M.D., Ph.D.,12 Alexander G. Bick, M.D., Ph.D.,13 Luca Malcovati, M.D.,14,15 Pradeep Natarajan, M.D., M.M.S.C.,2,9,10 and Benjamin L. Ebert, M.D., Ph.D.1,2,3,4,16
CHRS edifies earlier conclusions on CCUS
Objective hematologic parameter and mutational testing informs model

Weeks et al. NEJM Evid. 2023
Recurvise partitioning based on incidence of MN
Recurvise partitioning based on incidence of MN

Weeks et al. NEJM Evid. 2023
Model partitions well by CHRS risk of transformation

www.chrsapp.com

Weeks et al. NEJM Evid. 2023
Clonal Hematopoiesis and Inflammation in the Vasculature (CHIVE)

Cooperative Biorepository and Registry for CH

09 Dec 2023
MDS Foundation Breakfast Symposium - Annual American Society of Hematology Meeting, San Diego, CA
What is CHIVE?

- Registry following the natural history of CH
  - CH and *at risk* for CH
  - dB with clinical features captured

- Biorepository for storing samples for patients at risk/with CH
  - *Sequential* sample collection of peripheral blood, bone marrow (when available)
  - IRB approval for a variety of cellular assays and genotyping to further understand the pathophysiology of CH
CHIVEseq: Twist CH Assay

- This assay uses Twist bioscience hybrid capture technology to sequence coding sequences of 24 CHIP genes (or portions of genes) known to cause CHIP at >500x depth.

- The genes include: ASXL1, ASXL2, BRCC3, CBL, DNMT3A, ETNK1, GNAS, GNB1, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NRAS, PPM1D, SETBP1, SF3B1, SRSF2, TET2, TP53, U2AF1, ZBTB33, ZNF318.

- The assay can be run for as low as 1/10th cost of commercial sequencing panels.

CHIVE (ver1.0) Schema

**Approached for Consent**
(n=265)
- ≥18 years of age
- able to provide informed consent
- no active hematological malignancy

**Excluded**
- Did not meet criteria (n=36)
- Declined consent (n=47)
- Voluntary withdrawal (n=1)

**Enrolled from CH clinic (Arm A)**
(n=58)

**Enrolled due to risk for CH (Arm B)**
(n=123)

**Enrolled & Sequenced**
(n=181)

**CH+**
(n=99)

**CH-**
(n=82)

### Background

#### Demographics

- More male
- Older
- Trend to higher BMI

<table>
<thead>
<tr>
<th></th>
<th>CH - (n=82)</th>
<th>CH + (n=99)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (29.3)</td>
<td>50 (50.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Female</td>
<td>58 (70.7)</td>
<td>49 (49.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>3 (3.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>30-49</td>
<td>14 (17.1)</td>
<td>1 (1.0)</td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>27 (32.9)</td>
<td>24 (24.8)</td>
<td></td>
</tr>
<tr>
<td>65+</td>
<td>38 (46.3)</td>
<td>73 (74.2)</td>
<td></td>
</tr>
<tr>
<td>Median +/- IQR</td>
<td>62.9 (51.5 - 72.7)</td>
<td>71.9 (64.0 - 77.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Body Mass Index (BMI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>3 (3.7)</td>
<td>1 (1.0)</td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>23 (28.0)</td>
<td>22 (22.7)</td>
<td></td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>28 (34.2)</td>
<td>34 (35.1)</td>
<td></td>
</tr>
<tr>
<td>30.0 - 34.9</td>
<td>17 (20.7)</td>
<td>23 (23.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;35</td>
<td>11 (13.4)</td>
<td>17 (17.5)</td>
<td></td>
</tr>
<tr>
<td>Median +/- IQR</td>
<td>27.4 (24.1 - 32.4)</td>
<td>28.9 (25.4 - 32.1)</td>
<td>0.253</td>
</tr>
</tbody>
</table>

CHIVE – Gene Variant Frequencies similar to retrospective analyses

### CHIVE – Clinical features among CH⁺ and CH⁻ patients

<table>
<thead>
<tr>
<th>Blood Counts</th>
<th>CH⁻</th>
<th>CH⁺</th>
<th>Unit</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Blood Cells</td>
<td>6.8 (5.2 - 8.4)</td>
<td>6.2 (4.5 - 8.1)</td>
<td>x10⁹/mcL</td>
<td>0.455</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13.3 (12.3 - 14.6)</td>
<td>12.9 (11.4 - 14.1)</td>
<td>gm/dL</td>
<td>0.136</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>42.0 (37.0 - 44.0)</td>
<td>39.0 (35.0 - 43.0)</td>
<td>%</td>
<td>0.134</td>
</tr>
<tr>
<td>Platelet</td>
<td>245.0 (198.0 - 284.0)</td>
<td>203.0 (163.0 - 262.0)</td>
<td>x10⁹/mcL</td>
<td>0.093</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kidney Function</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>16.0 (12.0 - 21.0)</td>
<td>18.0 (14.0 - 23.0)</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.90 (0.76 - 1.11)</td>
<td>0.97 (0.84 - 1.29)</td>
<td>mg/dL</td>
</tr>
<tr>
<td>CKD Diagnosis, n(%)</td>
<td>15 (18.3)</td>
<td>41 (41.2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>97.0 (88.0 - 117.0)</td>
<td>106.0 (91.0 - 121.0)</td>
<td>mg/dL</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.0 (5.4 - 6.8)</td>
<td>5.8 (5.3 - 6.4)</td>
<td>%</td>
</tr>
<tr>
<td>Diabetes Mellitus Diagnosis, n(%)</td>
<td>22 (26.8)</td>
<td>32 (30.9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory Markers</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>16.0 (6.0 - 33.0)</td>
<td>20.0 (15.0 - 32.0)</td>
<td>mm/hr</td>
</tr>
<tr>
<td>CRP</td>
<td>3.2 (1.2 - 13.1)</td>
<td>8.2 (2.3 - 37.3)</td>
<td>mg/L</td>
</tr>
</tbody>
</table>

CHIVE – Clinical features among CH⁺ and CH⁻ patients indicate increased risk of vascular disease

<table>
<thead>
<tr>
<th>Cardiovascular Measurements</th>
<th>CH⁻</th>
<th>CH⁺</th>
<th>Unit</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure</td>
<td>125 (117-134)</td>
<td>129 (118-139)</td>
<td>mmHg</td>
<td>0.249</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>75 (68-82)</td>
<td>72 (66-78)</td>
<td>mmHg</td>
<td>0.177</td>
</tr>
<tr>
<td>Coronary Artery Disease Diagnosis, n(%)</td>
<td>27 (32.9)</td>
<td>55 (55.7)</td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Hypertension Diagnosis, n(%)</td>
<td>43 (52.4)</td>
<td>77 (79.4)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical Heart Failure Diagnosis, n(%)</td>
<td>8 (9.8)</td>
<td>24 (22.7)</td>
<td></td>
<td>0.035</td>
</tr>
<tr>
<td>Brain Natriuretic Peptide</td>
<td>79 (47-110)</td>
<td>56 (34-184)</td>
<td>pg/mL</td>
<td>0.908</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>60 (55-63)</td>
<td>61 (54-68)</td>
<td>%</td>
<td>0.424</td>
</tr>
</tbody>
</table>

High Risk Variants and progression to MDS/AML in CHIVE – Validation of ‘Big Data’ retrospective reports with new prospective analysis

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Number of Mutations</th>
<th>Mutation</th>
<th>Maximum VAF</th>
<th>High Risk Gene</th>
<th>Average VAF</th>
<th>Type of Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0004</td>
<td>4</td>
<td>TET2 R1516X</td>
<td>0.398</td>
<td>No</td>
<td>0.217</td>
<td>MDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TET2 Q695X</td>
<td>0.369</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRSF2 P95H</td>
<td>0.177</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>JAK2 V617F</td>
<td>0.02</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1060</td>
<td>1</td>
<td>SF3B1 R625C</td>
<td>0.241</td>
<td>Yes</td>
<td>0.236</td>
<td>MDS</td>
</tr>
<tr>
<td>1073</td>
<td>4</td>
<td>TET2 Q742X</td>
<td>0.422</td>
<td>No</td>
<td>0.237</td>
<td>CMML</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRSF2 P95R</td>
<td>0.330</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TET2 Y1245Lfs*22</td>
<td>0.270</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TET2 N535Kfs*6</td>
<td>0.033</td>
<td>No</td>
<td></td>
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<tr>
<td>1096</td>
<td>1</td>
<td>TET2 G1288D</td>
<td>0.796</td>
<td>No</td>
<td>0.758</td>
<td>CMML</td>
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<tr>
<td>2026</td>
<td>1</td>
<td>TP53 Y220C</td>
<td>0.676</td>
<td>Yes</td>
<td>0.676</td>
<td>AML</td>
</tr>
<tr>
<td>2038</td>
<td>1</td>
<td>TET2 Q749Rfs*15</td>
<td>0.021</td>
<td>No</td>
<td>0.021</td>
<td>MDS</td>
</tr>
</tbody>
</table>

CHIVE Rubric for testing

CH Mutation?

**High-Risk Criteria**
- Any mutation with a VAF ≥ 10%
- VAF < 10% with 2 or more variants
- CCUS (any VAF)
- High-risk mutations (any VAF)

**CH High-Risk**
- Collect samples every 6 months ±30 days from last deposit

**CH Low-Risk**
- Collect samples every 12 months ±90 days from last deposit

**No CH**
- Collect samples every 12 months ±90 days from last deposit
Summary and next steps

• Clonal hematopoiesis (CH) is an age-associated phenomenon and one of the most impactful conceptual discoveries across disciplines in medicine – we need to understand how to risk assess CHIP.

• Early prospective analysis (200 patients) illustrates similar patterns seen in retrospective data and in CHRS analysis.

• Large prospective international, multicenter participation is needed to properly understand risk.
3rd Annual Meeting of Somatic Mutations and Predisease

Addressing high risk clones

Nashville: October 25-26, 2024