Clonal Hematopoiesis

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Disclosures

I am on the scientific Advisory Board of TenSixteen Bio.
Although some things never change ... our genome does
Clonal Hematopoiesis

Silver, Bick, Savona, Nature Rev. Genetics 2021
WHO Classification of Haematolymphoid Tumours 5th edition

Clonal Hematopoiesis of Indeterminate Potential (CHIP)
- Myeloid driver mutation
- Variant Allele Fraction >2%
- No other blood abnormalities
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- No other blood abnormalities

Clonal cytopenia of undetermined significance (CCUS)

- CHIP + unexplained cytopenia

Aging
CHIP is common in the elderly

Vlasschaert [...] Bick, Blood 2023
Smoking demonstrates a dosage-dependent impact on risk of CH. CH associates with several smoking-related diseases. Contrary to published claims, we find no evidence that CH is associated with cardiovascular disease. We provide evidence that CH is driven by genes that are commonly mutated in myeloid neoplasia and implicate several new driver genes.
deCODE CH

a. mLOY

b. mCAs

Copy number gain

Copy number loss

Copy neutral loss of heterozygosity

c. CHIP

TET2

Mutant TET2
CHIP is associated with cardiovascular disease in the UK Biobank

Caitlyn Vlasschaert, Giulio Genovese, Yash Pershad, Siddhartha Jaiswal, Pradeep Natarajan, Alexander G. Bick

doi: https://doi.org/10.1101/2023.11.30.23299001
Myeloid Malignancy risk differs by CHIP gene

Weeks, NEJM Evidence 2023
Larger CHIP clones have worse outcomes
Larger CHIP clones have worse outcomes

Hypothesis:
Faster growth is worse than slower growth.
ASPREE-CHIP study

Participants: Community-dwelling age ≥70 or ≥65 US minorities

Intervention: randomization to 100mg aspirin daily or placebo

Main Outcomes and Measures: Disability-free survival, mortality, cancer and MACE

Median follow-up: 4.6 years
Observational f/u: 6.9 years

Zoe McQuilten, David Curtis
ASPREE-CHIP Investigators
ASPREE: Faster growth is worse than slower growth

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What causes CHIP?

**HSC Intrinsic**
- DNA damage
  - Aging
  - Smoking
  - Radiation exposure
  - Telomere attrition
  - DNA mismatch repair
- Germline genetics

**Selective pressures**
- Chemotherapy
- Immune-mediated marrow depletion
- Inflammation, infection, stress [...]


How are CHIP patients identified clinically?

**Incidental finding from solid tumor genetic testing**

<table>
<thead>
<tr>
<th>GENOMIC VARIANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biologically Relevant</strong></td>
</tr>
<tr>
<td>JAK2 p.V617F Missense variant - GOF</td>
</tr>
</tbody>
</table>

**Median Variant Allele Fraction**

| 3.3% |

**IMMUNOTHERAPY MARKERS**

**Microsatellite Instability Status**

MSI-High not detected

**TREATMENT IMPLICATIONS**

No reportable treatment options found.

Reported variant(s) detected in this patient's sample may be associated with clonal hematopoiesis or an underlying hematologic process. Clinical correlation is recommended.
How are CHIP patients identified clinically?

Incidental finding from solid tumor genetic testing

### GENOMIC VARIANTS

<table>
<thead>
<tr>
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<th>Variant Allele Fraction</th>
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<tr>
<td>JAK2 p.V617F Missense variant - GOF</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Median Variant Allele Fraction

Myeloid NGS panel during cytopenia workup

### TECHNICAL SUMMARY

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>AMP Tier</th>
<th>Chr</th>
<th>Pos</th>
<th>Ref</th>
<th>Alt</th>
<th>Coverage</th>
<th>Allele Freq. or Fold Change</th>
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</thead>
<tbody>
<tr>
<td>TET2</td>
<td>p.Gly1187Alafs*39</td>
<td>II</td>
<td>4</td>
<td>106164048</td>
<td>AG</td>
<td>A</td>
<td>14298</td>
<td>9%</td>
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<tr>
<td>Prognostic Variable</td>
<td>0.5</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>---------------------------------</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single <em>DNMT3A</em></td>
<td>present</td>
<td>absent</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High Risk Mutation</td>
<td></td>
<td>absent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation Number</td>
<td></td>
<td>1</td>
<td></td>
<td>≥ 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variant Allele Fraction</td>
<td></td>
<td>&lt; 0.2</td>
<td></td>
<td>&gt; 0.2</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Red Cell Distribution Width</td>
<td></td>
<td>&lt; 15</td>
<td></td>
<td></td>
<td>≥ 15</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean Corpuscular Volume</td>
<td></td>
<td>&lt; 100</td>
<td></td>
<td></td>
<td>&gt; 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenia</td>
<td></td>
<td>CHIP</td>
<td>CCUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age</td>
<td></td>
<td>&lt; 65y</td>
<td>≥ 65y</td>
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</tbody>
</table>
Clonal Hematopoiesis Risk Score (CHRS) Calculator

Patient Characteristics

CHIP or CCUS
Number of mutations
Maximum VAF
Mean corpuscular volume (MCV)
Red cell distribution width (RDW)
Age

About this calculator  CHRS Score and Clinical Outcomes  Population Data

The clonal hematopoiesis risk score (CHRS) is a prognostic model for clonal hematopoiesis of indeterminate uncertain significance (CCUS) which can be used to estimate 5- and 10-year cumulative risk of myeloid malignancy data published in Weeks LD et al. 2023. New England Journal of Medicine Evidence. The CHRS was developed using patient cohorts from Dana-Farber Cancer Institute, Boston, MA, USA and University of Washington.

Cytopenia definitions in CCUS:
- anemia: hemoglobin < 12g/dL for females, <13 g/dL for males
- thrombocytopenia: platelet count < 150 K/uL
- neutropenia: absolute neutrophil count < 1.8 K/uL

Using the CHRS calculator:
- Outcome predictions are made using data/variables obtained at the time of next generation sequencing.
- Select a diagnosis of CHIP or CCUS.
- Select the number of pathogenic somatic variants (mutations) detected by peripheral blood or bone marrow
- For patients with only 1 mutation, indicate whether the mutated gene is DNM73A (single DNM73A). This field defaults to 'Absent' for patients with multiple mutations.
- Indicate whether there are mutations in high risk genes (SF3B1, SRSF2, ZRSR2, JAK2, TP53, RUNX1) This field defaults to 'Absent' when single DNM73A mutations is selected.
- Indicate if the maximum variant allele fraction (VAF) - for any mutation - is ≥ 0.2 (20%)
- Indicate whether mean corpuscular volume (MCV) is ≥ 100 femtoliters, red cell distribution width is ≥ 15%

After entering patient information, click 'Calculate CHRS'.
Weeks, NEJM Evidence 2023

**Number at Risk**

<table>
<thead>
<tr>
<th>Time (yr)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
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</thead>
<tbody>
<tr>
<td>High risk</td>
<td>123</td>
<td>113</td>
<td>101</td>
<td>86</td>
<td>76</td>
<td>63</td>
<td>25</td>
</tr>
<tr>
<td>Int. risk</td>
<td>1,196</td>
<td>1,176</td>
<td>1,141</td>
<td>1,101</td>
<td>1,051</td>
<td>1,005</td>
<td>354</td>
</tr>
<tr>
<td>Low risk</td>
<td>10,018</td>
<td>9,963</td>
<td>9,830</td>
<td>9,717</td>
<td>9,567</td>
<td>9,386</td>
<td>3,793</td>
</tr>
<tr>
<td>No CHIP/CCUS</td>
<td>182,406</td>
<td>181,706</td>
<td>180,486</td>
<td>178,864</td>
<td>76,967</td>
<td>174,688</td>
<td>72,376</td>
</tr>
</tbody>
</table>

No CHIP/CCUS: 10-year survival = 95.8±0.0471%
Low risk: 10-year survival = 93.7±0.243%
Intermediate risk: 10-year survival = 84.0±1.06%
High risk: 10-year survival = 51.2±4.51%
Ongoing Clonal Hematopoiesis Clinical Trials

There are no FDA approved therapies for CHIP

Targeting Specific Driver Mutations

• Ivosidenib for Patients With Clonal Cytopenia of Undetermined Significance and Mutations in IDH1 [NCT05030441]
• A Study of Enasidenib in People With Clonal Cytopenia of Undetermined Significance [NCT05102370]

Targeting bone marrow environment

• Canakinumab for the Prevention of Progression to Cancer in Patients With Clonal Cytopenias of Unknown Significance, IMPACT Study [NCT05641831]
The under-appreciation of CHIP

It's time to drop the "indeterminate" and get serious about this biomarker

ERIC TOPOL
MAY 21, 2023

Each day the 50,000 to 200,000 blood stem cells in our bone marrow, known as hematopoietic (HSC), produce billions of specialized blood cells—red blood cells, platelets, B and T lymphocytes, and various myeloid cells (white blood cells, such as neutrophils and monocytes). As we age, the repeated cell divisions of the HSCs lead to acquired ("somatic") mutations. When such a mutation of an HSC leads to a clone that expands—which denotes some fitness advantage—it is known as clonal hematopoiesis. CHIP, which stands for clonal hematopoiesis of indeterminate potential, refers to presence of myeloid blood cells with a driver gene mutation (with a frequency of ≥ 2%) without any clinical criteria of a blood cancer. It turns out CHIP is a major biomarker, not just for blood cancer (an 11-fold risk of a blood malignancy, or absolute 0.5% risk per year), but also for heart disease, blood clot events such as stroke and pulmonary embolism, and many other chronic illnesses (simplified Figure below).
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