Clinical Implications of Clonal Hematopoiesis

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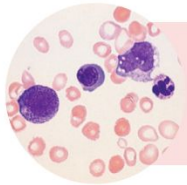
Disclosures

- None

5th edition of the WHO (2022)



Myeloid proliferations & neoplasms

Myeloid precursor lesions (NEW)	Myelodysplastic neoplasms	Acute myeloid leukemia
Clonal Haematopoiesis	Myelodysplastic neoplasms with defining genetic abnormalities	Acute myeloid leukemia with defining genetic abnormalities
Clonal haematopoiesis of indeterminate potential (CHIP)	Myelodysplastic neoplasms morphologically defined	Acute myeloid leukemia, defined by differentiation
Clonal cytopenia of undetermined significance (CCUS)	Myelodysplastic neoplasms of childhood	Myeloid sarcoma

Myeloid precursor lesions added to WHO 2022, CHIP and CCUS formally defined

Clonal Hematopoiesis of Indeterminate Potential

- (WHO) Classification defined CHIP as the presence of a somatic mutation associated with myeloid neoplasia detected in the peripheral blood or bone marrow with a VAF ≥ 2% in the absence of definitive morphologic evidence of a hematologic disorder
  - Dominate mutations: TP53, TET2, DNMT3A, ASXL1, JAK2

- Prevalence of CH increases with age – 10%-15% of 60 to 70 years of age
  - With a VAF of ≥0.01% the prevalence of CH to be nearly ubiquitous in persons >50 years of age

- CH is 5 to 10 times higher in patients who have received cytotoxic chemotherapy or ionizing radiation

- CHIP is associated with decreased overall survival, increased risk for a hematologic malignancy, and cardiovascular complications, compared with age-matched individuals without CHIP
  - Increase mortality occurred in those 70 +years old, not younger individuals
  - Excessive mortality is driven by cardiovascular events rather than hematologic neoplasms

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CHIP and Hematologic Malignancies

- CHIP is associated with an increased risk of transformation to myeloid neoplasms

- Only a small fractions of individuals with CHIP will develop hematologic malignancies
  - Risk of evolution to AML is estimate at 0.5% to 1% per year
  - Prevalence in 70year-olds is 100-fold greater than prevalence or MDS or leukemia

- Risk factors for developing myeloid malignancies
  - Age 65 years or greater
  - High-risk mutations (*SF3B1, SRSF2, ZRSR2, JAK2, TP53, RUNX1, FLT3, IDH1, or IDH2).*
  - VAF ≥20 percent
  - ≥2 distinct mutations
  - Cytopenias
  - RBC indices (RDW ≥15 percent or MCV >100 fL)

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Clonal Hematopoiesis Risk Score (CHRS)

Prognostic Variable	0.5	1	1.5	2	2.5
Single *DNMT3A*	present	absent	–	–	–
High Risk Mutation	–	absent	–	–	present
Mutation Number	–	1	–	≥ 2	–
Variant Allele Fraction	–	< 0.2	–	> 0.2	–
Red Cell Distribution Width	–	< 15	–	–	≥ 15
Mean Corpuscular Volume	–	< 100	–	–	> 100
Cytopenia	–	CHIP	CCUS	–	–
Age	–	< 65y	≥ 65y	–	–

Risk	% of patients	% 10yr survival
Low	88.4%	93.7%
Intermediate	10.5%	84.0%
High	1.1%	51.2%

Weeks L, Niroula A, Neuberg D et al Prediction of Risk for Myeloid Malignancy in Clonal Hematopoiesis NEJM Evid 2023;2(5)

Risk-Stratification Model to Predict Progression of MGUS to MM or Related Disorders

Risk Group	Relative Risk	Absolute Risk of Progression (20 Years), %	Absolute Risk of Progression (20 Years), Accounting for Death as a Competing Risk, %
Low – no risk factors present (39% of patients)	1	5	2
Low-intermediate – 1 risk factor present (37% of patients)	5.4	21	10
High-intermediate – 2 risk factors present (20% of patients)	10.1	37	18
High – all 3 risk factors present (4% of patients)	20.8	58	27

Adapted from *Blood*. 2005;106:812-817

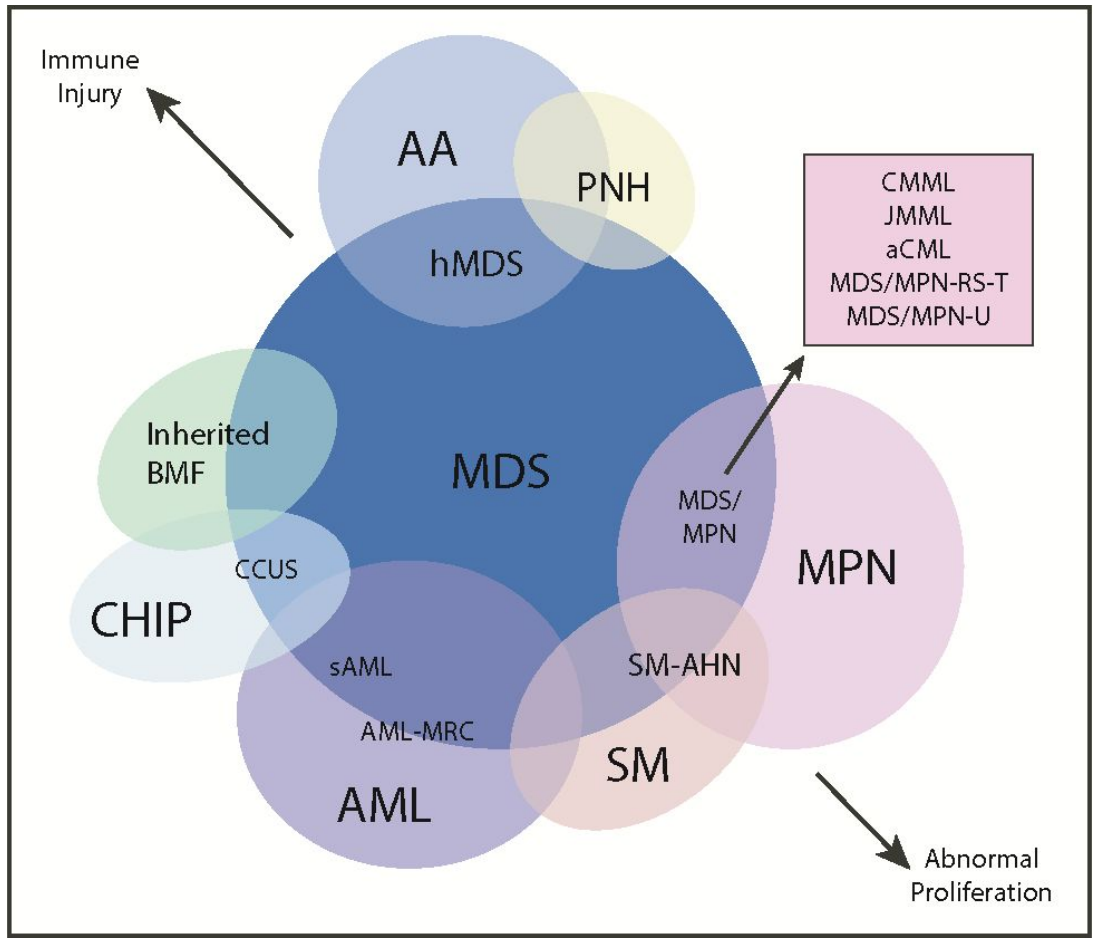
MGUS

- Prevalence in general population
  - >50year 3.4%, >70year 5.3%, >80year 7.5%
- Mean age of dectection 70 years
- Only 1% of patients go on to develop myeloma in a year
- Lifetime risk of progression ~10%
- Virtually all malignant plasma cell dyscrasias are preceded by MGUS
- Median survival of individuals only slightly shorter than that of age-matched controls

Monitoring

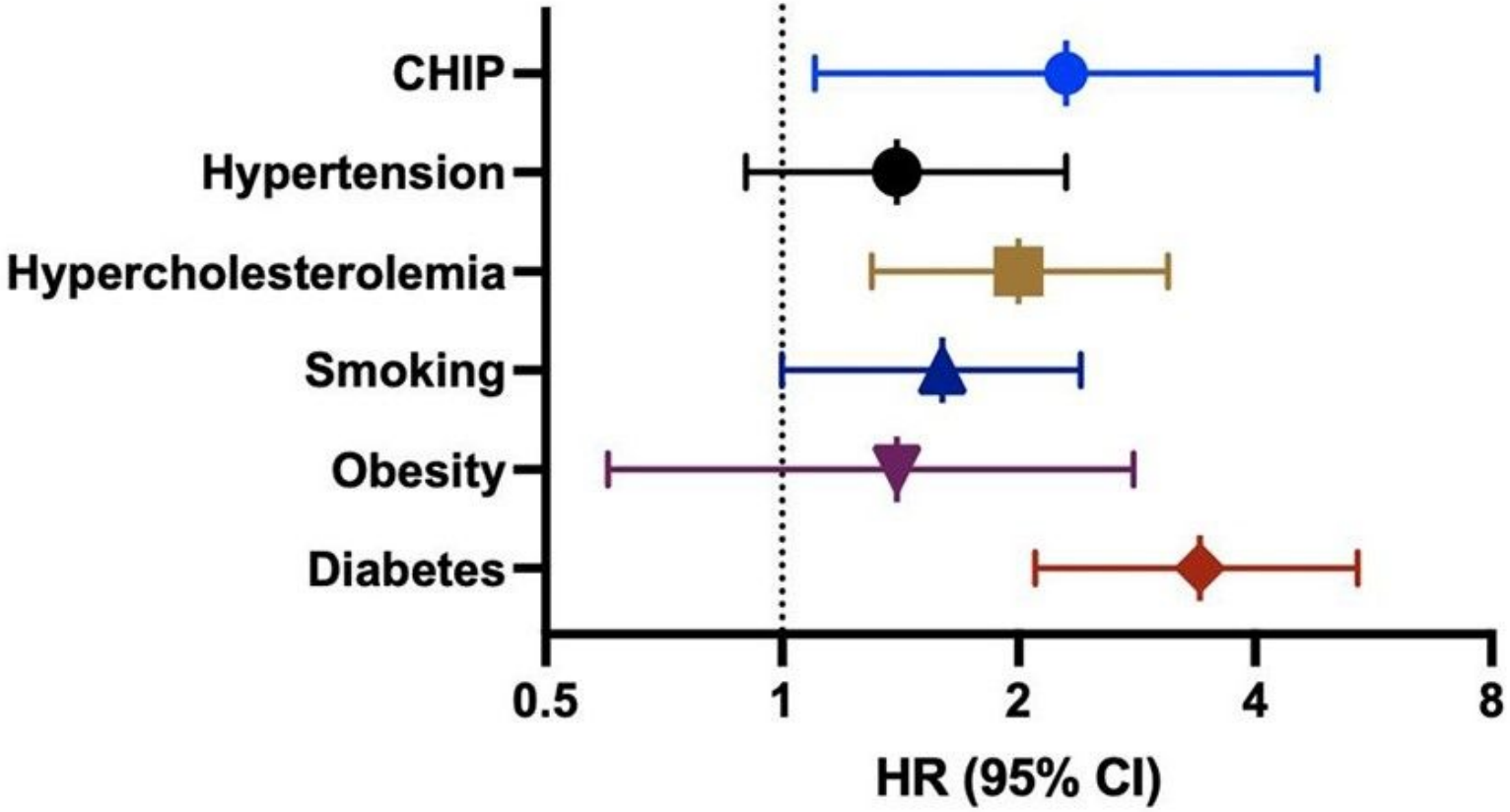
- Screening is not recommended
- No prospective studies to proven the benefits of monitoring
- Observational studies of population-based cohorts with MGUS
  - associated with improved survival and less morbidity in those who progress to myeloma
  - Unclear whether this benefit was due to earlier detection and initiation of treatment or lead-time bias.

MDS overlap disorders and diagnostic boundaries



Tiffany N. Tanaka,Rafael Bejar, MDS overlap disorders and diagnostic boundaries, Blood, 2019,

Adjusted HR for incident CHD among Jackson Heart Study & FUSION participants



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Clonal hematopoiesis of indeterminate potential (CHIP): Linking somatic mutations, hematopoiesis, chronic inflammation and cardiovascular disease. J Mol Cell Cardiol. 2021 Dec;161:98-105.

Clinical Interpretation – The Next Bottleneck

A major goal of cancer genomics is identifying "actionable" mutations that drive a tumor and can be targeted with available therapy **BUT**…

"Then you have a 5-inch-thick set of papers on your desk for the bioinformatics.

That's where the cost is."

(Gail Vance, Director of Diagnostic Genomics, Indiana U. School of Medicine)

- Ever-increasing amount of data growing complexity for physicians & patients to process
  - NGS data • MDx & pathology results • Growing body of cancer & biomarker literature • New targeted therapies • Combination therapy • Clinical Trials
- Physicians will need greater information on the appropriate integration of molecular testing into treatment decision making.

Thanks

Hello, here is my tumor sequence