Myelodysplastic Syndromes: Update on Classification and Distinction from Non-Neoplastic Entities

Robert P Hasserjian, MD
Associate Professor
Massachusetts General Hospital and Harvard Medical School

Overview of lecture

- Review evolving concepts in diagnosing and classifying MDS
  - Distinguishing MDS from non-neoplastic conditions that cause cytopenia
  - Distinguishing MDS from AML
  - Classifying MDS to optimally risk stratify patients for clinical management
- Present upcoming changes to the revised 2016 WHO MDS classification
  - Influence of new molecular genetic data

Myelodysplastic syndromes

- Clonal hematopoietic stem cell diseases
  - At diagnosis, the vast majority of hematopoietic cells are part of the neoplastic clone
  - Clone has recurring genetic abnormalities
- Ineffective hematopoiesis with one or more peripheral cytopenias
- Morphologic dysplasia of maturing hematopoietic elements
- Variable increase in myeloblasts (<20%)
The spectrum of MDS

- **Indolent “low-grade” subtypes**
  - Low blast counts
  - Typically low risk of progression to AML
  - Morbidity and mortality due to cytopenias and/or complications of transfusion

- **Aggressive subtypes**
  - Higher blast counts, genetic instability
  - Often rapidly progress to AML

Challenges in MDS diagnosis

- **Low-grade**
  - Non-neoplastic causes of cytopenia
    - Other neoplasms
    - Inherited
    - Extrinsic factors
  - Does the patient have a neoplasm?
  - Should the patient be treated for MDS or should another diagnosis be sought?

- **High-grade**
  - Risk-adapted therapy according to prognosis
  - Should the patient receive induction or other intensive chemotherapy with a goal of remission?
Involvement of the pathologist in diagnosing MDS

- Patient comes to clinical attention due to cytopenia
- Hematologist evaluates the patient
  -- Identifiable secondary cause of cytopenia?
  -- Would the patient be treated if MDS is diagnosed?
- Clinical information
- Peripheral blood and marrow morphology
- Flow cytometry
- Cytogenetics
- Molecular genetics
- Bone marrow biopsy and aspirate are performed

Ingredients of MDS diagnosis and classification (2008 WHO)

- Unexplained cytopenias are a sine qua non of MDS
- Prognostic
- Peripheral counts
- If present, MDS-specific cytogenetic abnormalities provide proof of clonality
- Prognostic
- Dysplasia and blasts
  - Dysplasia is a sine qua non of MDS
  - Both are prognostic

MDS: Low power morphologic abnormalities

- Hypercellular marrow (80% of cases)
- Disorganization of hematopoiesis
  - Immature myeloid elements occur away from bone trabeculae
  - Erythroid elements fail to form well-defined clusters
- Often many small, hypolobated megakaryocytes

Architectural disorganization in MDS
Maintained architecture in reactive marrow hyperplasia (ARH)
Megakaryocyte dysplasia

- Small size
- Hypo/mononucleation
- Separated nuclear lobes

Myeloid lineage dysplasia

- Bilobed pseudo Pelger-Huet nucleus
- Nuclear hypersegmentation or other abnormal nuclear shape
- Cytoplasmic hypogranulation or uneven granulation

Erythroid lineage dysplasia

- Megaloblastoid change (nuclear:cytoplasmic asynchrony)
- Cytoplasmic vacuolization
- Bi- or multi-nucleation
- Nuclear budding and nuclear irregularities, pyknosis
Problems with using morphologic dysplasia to diagnose MDS

- 10% threshold to call a lineage dysplastic
- No distinction between different dysplastic morphologies
- Dysplasia is not always reproducible among pathologists
- Dysplasia is not specific for MDS
  - Significant dysplasia present in bone marrow of normal volunteers
  - Dysplastic changes are even more frequent in patients with non-neoplastic cytopenias


Situations to think twice before diagnosing MDS

- History of drugs/toxins
  - Recent (<6 months) chemotherapy
  - Heavy alcohol intake
- Metabolic deficiencies: B12, folate, copper
- ‘Stress erythropoiesis’ due to hemoglobinopathies or acquired/congenital hemolytic anemias
- Infections, especially HIV and Hepatitis C
- Autoimmune diseases
- Concurrent neoplasms
  - Infiltrating marrow, especially hairy cell leukemia and myeloma
  - Rarely paraneoplastic dysplasia from remote solid tumor
- Beware of making the diagnosis in young patients!


Neoplastic versus ‘reactive’ dysplasia

- Normal stem cell AND Normal microenvironment
  - YIELDS Normal progeny
- Normal stem cell AND Abnormal microenvironment
  - YIELDS Dysplastic progeny


Not MDS


Castello A et al. Haematologica 1992;77:392
Can we do better than ≥10%?

| Morphologic abnormality* | Cutoff value* | AUC | Cohen’s K coefficient
|--------------------------|--------------|-----|---------------------|
|                         |              |     | Inter-observer agreement
| **Erythroid lineage**    |              |     |                     |
| Megablastoid changes    | > 5%         | 0.814, P < 0.001 | 0.83 |
| Is- or multinucleated    | > 5%         | 0.679, P < 0.001 | 0.87 |
| Nuclear lobulation or irregular contours | > 5% | 0.600, P < 0.0001 | 0.84 |
| Pyknotic nucleus         | > 5%         | 0.677, P < 0.001 | 0.81 |
| Cytoplasmic fraying      | > 5%         | 0.602, P < 0.001 | 0.82 |
| Ring sideroblasts        | > 5%         | 0.650, P < 0.0001 | 0.95 |
| - 15%                    | 0.719, P < 0.001 | 0.92 |
| **Granulocytic lineage** |              |     |                     |
| Myeloblasts              | > 5%         | 0.727, P < 0.001 | 0.92 |
| Auer rods                | > 5%         | 0.723, P < 0.001 | 0.90 |
| - 1%                     | 0.524, P < 0.001 | 0.90 |
| Abnormal nuclear shape   | > 5%         | 0.814, P < 0.001 | 0.86 |
| Neutrophil hypogranulation | > 3%       | 0.700, P < 0.0001 | 0.86 |
| - 3%                     | 0.791, P < 0.0001 | 0.81 |
| **Megakaryocytic lineage** |       |     |                     |
| Micromegakaryocytes      | > 5%         | 0.916, P < 0.001 | 0.88 |
| Small binucleated megakaryocytes | > 5% | 0.845, P < 0.001 | 0.81 |
| Megakaryocytes with multiple separated nuclei | > 5% | 0.750, P < 0.001 | 0.84 |
| Hypolobated or monolobular megakaryocytes | > 5% | 0.646, P < 0.0001 | 0.86 |

Morphologic diagnosis of MDS remains subjective

- Morphologic dysplasia
  - ↑ Lineages involved
  - ↑ Number of dysplastic forms
  - ↑ Severity of dysplasia
  - Severity and persistence of cytopenia(s) (>6 months)

Younger patients
Co-morbid conditions
Paucity of clinical history

What if it’s not clearly MDS, but there’s no specific diagnosis?

- A common occurrence in the workup of the cytopenic patient!
  - 60-80% of cytopenic patients undergoing BM exam
- Anemia of chronic inflammation
  - Often increased iron in marrow histiocytes
- Reactive causes which may or may not become evident later
  - Test of time: transient causes often resolve
- Early MDS cases which are not well-developed enough for definitive diagnosis
  - Test of time: cytopenia is refractory or worsens
  - OK to hedge on initial marrow in these situations

Morphologic evaluation of dysplasia in the 2016 update

- Dysplasia threshold will be kept at 10% for all lineages, but will note that 30% or 40% level for megakaryocytes may be more specific
  - Emphasis on micromegakaryocytes as a highly specific morphologic finding for MDS
- Emphasis on morphologic overlap with non-MDS mimics (always a potential pitfall!)
**Idiopathic cytopenia of undetermined significance**

- ICUS designation proposed for patients with prolonged, unexplained cytopenia(s) who do not fulfill MDS diagnostic criteria
  - Insufficient dysplasia and normal karyotype
- These patients should be followed
  - Some will eventually be diagnosed with MDS
  - In others, another cause for cytopenia will emerge
  - Some remain with persistent, stable cytopenia and no identifiable cause

**Can we develop a more objective way to diagnose MDS?**

- Genetic abnormalities
  - Karyotype abnormalities
  - Sub-karyotypic acquired genetic alterations
    - Microdeletions (SNP array)
    - Mutations (next-generation sequencing)
- Flow cytometry abnormalities
  - Hematopoiesis in most MDS cases is phenotypically abnormal

**Utility of MDS flow cytometry assessment**

- Accumulating evidence suggests that abnormal flow cytometry patterns predict MDS with good sensitivity/specificity
- Only considered as “supportive” of MDS, not sufficient for making a primary MDS diagnosis by WHO 2008/2016

**MDS-defining cytogenetic abnormalities (WHO)**

<table>
<thead>
<tr>
<th>Cytogenetic Abnormality</th>
<th>Unbalanced</th>
<th>Primary MDS</th>
<th>Therapy-related MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7 or del(7q)</td>
<td>10%</td>
<td>10%</td>
<td>50%</td>
</tr>
<tr>
<td>-5 or del(5q)</td>
<td>10%</td>
<td>3-5%</td>
<td>40%</td>
</tr>
<tr>
<td>i(17q) or t(17p)</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>-13 or del(13q)</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>del(11q)</td>
<td>3%</td>
<td>1-2%</td>
<td></td>
</tr>
<tr>
<td>del(12p) or t(12p)</td>
<td>3%</td>
<td>1-2%</td>
<td></td>
</tr>
<tr>
<td>del(9q)</td>
<td>3%</td>
<td>1-2%</td>
<td></td>
</tr>
<tr>
<td>idic(X)(q13)</td>
<td>1-2%</td>
<td>1-2%</td>
<td></td>
</tr>
</tbody>
</table>

**Flow Cytometry Abnormality in 50% of MDS cases**

- CD16 F IT C-A
- CD13 F APC-A
- CD7 F IT C-A
- CD34 P ERC P-Cy5-5-A

**Cytogenetic Abnormality in 50% of MDS cases**

- t(11;16)(q23;p13.3) 3%
- t(3;21)(q26.2;q22.1) 2%
- t(1;3)(p36.3;q21.2) 1%
- t(2;11)(p21;q23) 1%
- inv(3)(q21q26.2) 1%
- t(6;9)(p23;q34) 1%
Somatic mutations in MDS: a barrage of new information!

- Ribosomal proteins: RPS14
- Epigenetic regulators: TET2, ASXL1
- RNA splicing: SF3B1, SRSF2, U2AF1
- Transcription factors: RUNX1, ETV6
- Tyrosine kinase signaling: RAS
- Tumor suppressor genes: TP53

At least one recurrent genetic abnormality is found in 80-92% of MDS cases at diagnosis.

Mutations in 738 MDS patients

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Can mutations be used to diagnose MDS in 2015?

- Beware: 10% of healthy individuals >65 years harbor somatic MDS-type mutations in hematopoietic cells! (“CHIP”)
  - DNMT3A, TET2, ASXL1, TP53, JAK2, SF3B1
  - Allele burden typically 10-20% in blood, can be higher
  - Associated with increased risk of subsequent hematologic malignancy and death

- Presence of mutations is not sufficient to diagnose MDS: further study is needed

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Both CHIP and MDS affect older individuals, but CHIP is more frequent

- Incidence of MDS per 100,000
- Frequency of CHIP

CHIP: “Clonal Hematopoiesis of Indeterminate Potential”

- Flow cytometry abnormalities
- SF3B1 mutation
  - Strongly associated with ring sideroblasts, which makes diagnosis of MDS easy!
- More mutations (2 or more)
- Higher variant allele fraction
- Further study needed to understand how to interpret mutational profiles

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Features that may indicate higher likelihood of MDS
**What is sufficient to diagnose MDS in a cytopenic patient in 2016?**

<table>
<thead>
<tr>
<th>Observation</th>
<th>Sufficient to diagnose MDS in isolation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplastic morphology (≥10%)</td>
<td>Yes, provided possible secondary causes of cytopenia and dysplasia are excluded clinically</td>
</tr>
<tr>
<td>Excess marrow blasts (≥5%)</td>
<td>Yes, provided marrow recovery or growth factor effect are excluded</td>
</tr>
<tr>
<td>Cytogenetic abnormality</td>
<td>Yes, provided it is on the WHO list of ‘approved’ abnormalities*</td>
</tr>
<tr>
<td>Flow cytometry abnormality</td>
<td>No, but can support an MDS diagnosis suspected by other observations</td>
</tr>
<tr>
<td>MDS-type mutation</td>
<td>No, these can be found in normal individuals and more study is needed (&quot;Clonal hematopoiesis of indeterminate potential&quot;)</td>
</tr>
</tbody>
</table>

*Specifically excluded are −Y, +8, and del(20q)

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**Challenges in MDS diagnosis**

Low-grade

High-grade

MDS

AML

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**20% blasts defines the border of MDS versus AML but...**

- The 20% threshold may not be as relevant in some situations
  - Therapy-related myeloid neoplasms
  - Certain genetic abnormalities, e.g. t(3;3) and inv(3), MLL rearrangement, TP53 mutation
  - AML with relatively stable blast count of 20-30%
- Possible surrogates for blast count
  - Tempo of disease, mutational profile

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**The border between MDS and AML: Acute erythroid leukemia (AEL, M6A)**

- Erythroid elements are ≥50% of marrow cells
  - Calculate blasts as % of the non-erythroid cells: if ≥20%, then diagnosis is AEL
- AEL is a subtype of AML, but recent data suggest a closer relationship to MDS
  - Often occurs as a “progression” of prior MDS
  - Morphologic dysplasia is characteristic
  - Genetic abnormalities more similar to MDS
    - TP53 mutation common, FLT3/NPM1 mutations rare

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Blast counting in myeloid neoplasms with erythroid predominance

- Small changes in blast percentages can change diagnosis, with major clinical impact

MDS or acute erythroleukemia?

- Erythroids may fluctuate due to therapy, metabolic deficiencies, or EPO effects → changed diagnosis

?RAEB<>AEL?
AEL patients probably do not benefit from intensive chemotherapy

- 75 de novo AEL
- 40 RAEB-E (≥50% erythroids)
- 230 RAEB-N (<50% erythroids)

Overall survival of AEL, RAEB-E and RAEB-N

Wang SA et al. Mod Pathol 2015 (abstract)

WHO 2016: Non-erythroid blast counting will be eliminated

- Cases with ≥50% erythroids and 5-19% blasts will be considered as MDS, no longer AML
  - Cases with ≥20% blasts and ≥50% erythroids will still be classified as AML
- Will achieve consistency of blast counting across all myeloid neoplasms
  - Avoid abrupt change when erythroids reach 50%
- Will link AEL with MDS, with which it shares morphologic and genetic features

Challenges in MDS diagnosis

Low-grade
- Non-neoplastic causes of cytopenia
  - Other neoplasms
    - Inherited
    - Extrinsic factors

High-grade

MDS

AML

Accurate classification to optimize risk-adapted therapy

WHO MDS subtypes (2008)

<table>
<thead>
<tr>
<th>No excess of blasts</th>
<th>Excess blasts</th>
</tr>
</thead>
</table>
| Refractory anemia with ring sideroblasts (RARS) | Refractory anemia with excess blasts
| Refractory cytopenia with unilineage dysplasia (RCUD) | - RAEB1
| Refractory cytopenia with multilineage dysplasia (RCMD) | - RAEB2
| MDS with isolated del(5q) | MDS, unclassifiable (MDS-U) |
### Prognostic schemes in MDS

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia</td>
<td>Yes: single versus multilineage and ring sideroblasts</td>
<td>No</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>Yes: Pancytopenia is only defining feature</td>
<td>Yes: both number and depth of cytopenias</td>
</tr>
<tr>
<td>Blast % in blood</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Blast % in bone marrow</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Yes: isolated del(5q) is the only defining feature</td>
<td>Yes, 5 prognostic groups</td>
</tr>
<tr>
<td>Molecular genetic abnormalities</td>
<td>Yes (SF3B1 mutation)</td>
<td>No</td>
</tr>
<tr>
<td>Flow cytometry abnormalities</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Revised International Prognostic Scoring System of MDS

### Blast count in MDS is critical for prognostic stratification


### Refractory anemia with excess blasts

- Dysplastic promyelocyte
- Blasts

### Dysplastic erythroids (MDS) and Early erythroids and blast
Role of blast estimation in the biopsy

- In some situations, the core biopsy blast count may be more accurate than the aspirate count
  - Hypocellular marrow
  - Fibrotic marrow
  - Technically poor aspirate smear
- CD34 immunostain may be effectively used to estimate blasts in the biopsy/clot section
- Some experts advocate performing CD34 on all bone marrow biopsies where MDS is a diagnostic consideration

Prognostic influence of cytogenetic abnormalities in MDS

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Cytogenetic abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>Single del(11q) or -Y</td>
</tr>
<tr>
<td>Good</td>
<td>Normal del(5q)(single or with 1 other)</td>
</tr>
<tr>
<td></td>
<td>Single del(12p) or del(20q)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, i(17q), +19, single del(7q)</td>
</tr>
<tr>
<td></td>
<td>Any other single or double</td>
</tr>
<tr>
<td>Poor</td>
<td>-7, inv(3), t(3q), del(3q)</td>
</tr>
<tr>
<td></td>
<td>del(7q) with 1 other</td>
</tr>
<tr>
<td></td>
<td>3 separate abnormalities</td>
</tr>
<tr>
<td>Very poor</td>
<td>4 or more separate abnormalities (complex)</td>
</tr>
</tbody>
</table>


MDS with isolated del(5q): 2008 definition

- Del(5q) is only cytogenetic abnormality
- Blasts <5% in bone marrow, <1% in blood
- Can have any cytopenias; often thrombocytosis
- Can have uni- or multilineage dysplasia
  - Typically striking dysplasia of megakaryocytes and relative erythroid hypoplasia
- Favorable prognosis and excellent response to lenalidomide
MDS with isolated del(5q)

No adverse effect with one additional cytogenetic abnormality

TP53 mutation confers poor prognosis to del(5q) patients treated with lenalidomide

Changes to MDS del(5q) in the 2016 update

- Broaden definition to allow one additional cytogenetic abnormality (except -7 or del7q)
- Suggest TP53 mutation test or p53 immunostain for prognostic information
- Any cases with increased blasts in blood or bone marrow are still excluded from the MDS del(5q) category

P53 immunohistochemistry correlates well with presence of TP53 mutation
- >1% positive cells in marrow
- Strongly correlated with poor prognosis in all types of MDS

Cleven AJ et al. Mod Pathol 2015;28:552

Specific mutations also carry prognostic impact. Bejar R NEJM 2011;364:2496.

- TP53, EZH2, ETV6, RUNX1 mutations confer adverse prognosis.
- ASXL1 mutation is associated with a survival advantage in MDS.

**SF3B1**: a spliceosome gene where mutation conveys a favorable prognosis.

- Strongly correlates with the presence of ring sideroblasts (>98%).
- Appears to be an early founding mutation in MDS.
- Confers a survival advantage in MDS.

**Ring sideroblasts**: erythroid forms with aberrant iron accumulation in mitochondria encircling the nucleus.

**SF3B1 mutation is associated with highly differential gene expression**.

- Includes downregulation of ABCB7 gene due to altered exon usage.

New handling of MDS with ring sideroblasts in WHO 2016

- MDS with ring sideroblasts (MDS-RS) will be broadened to include:
  - Traditional RARS (single lineage dysplasia)
  - Cases with multilineage dysplasia
  - Cases with SF3B1 mutation and ≥5% RS
    - If SF3B1 mutation status is negative or unknown, ≥15% RS will be required
- Presence of SF3B1 mutation or RS will not affect RAEB or MDS with isolated del(5q)

Why change MDS nomenclature?

- WHO scheme classifies on dysplasia and blast counts, not cytopenia: so why put cytopenia in the name?
  - Cytopenias are already captured in IPSS-R
- Type of dysplasia often does not agree with the cytopenic lineage in single-lineage dysplasia MDS
  - Cannot predict peripheral counts from dysplasia
  - Subgroups of refractory anemia, refractory neutropenia, and refractory thrombocytopenia will be eliminated

New WHO MDS nomenclature

- MDS with ring sideroblasts (± SF3B1 mutation)
  - And single lineage dysplasia
  - And multilineage dysplasia
- MDS with single lineage dysplasia
- MDS with multilineage dysplasia
- MDS with excess blasts-1
- MDS with excess blasts-2

New WHO Classification of MDS (<5% blasts)

- MDS with single lineage dysplasia (MDS-SLD)
  - Only one lineage is dysplastic
  - 1-2 cytopenias
    - May not necessarily correlate with dysplastic lineage!
  - Good prognosis
- MDS with multilineage dysplasia (MDS-MLD)
  - Two or three dysplastic lineages
  - 1-3 cytopenias
  - Intermediate prognosis

New WHO Classification of MDS (<5% blasts)

- MDS with ring sideroblasts (MDS-RS)
  - ≥15% ring sideroblasts on iron stain
  - OR
  - ≥ 5% ring sideroblasts and an SF3B1 mutation
  - Usually few other mutations and simple karyotype
  - Will be further divided based on single (MDS-RS-SLD) versus multilineage (MDS-RS-MLD) dysplasia

New WHO Classification of MDS (≥5% blasts)

- MDS with excess blasts (MDS-EB)
  - Increased blasts are a very strong indicator of aggressive behavior in MDS, independent of cytogenetics, cytopenias, and mutations
  - Defined by blast percentages in both the bone marrow and the blood
  - CD34 useful in cases with fibrosis or poor aspirate
  - Blast count is now always based on the total cells—not the non-erythroid cells
  - Most cases of ‘acute erythroleukemia’ are now MDS-EB

Summary: MDS revision

No excess of blasts
- MDS with single lineage dysplasia
- MDS with multilineage dysplasia
- MDS with ring sideroblasts
  - and unilineage dysplasia
  - and multilineage dysplasia
- MDS with isolated del(5q)
- MDS, unclassifiable (MDS-U)

Excess blasts
- MDS with excess blasts
  - MDS with excess blasts-1
  - MDS with excess blasts-2

Either ≥15% RS or ≥5% RS and SF3B1 mutation

One additional chromosomal abnormality allowed

Recommend testing for TP53 mutation

Summary: MDS revision

No excess of blasts
- MDS with single lineage dysplasia
- MDS with multilineage dysplasia
- MDS with ring sideroblasts
  - and unilineage dysplasia
  - and multilineage dysplasia
- MDS with isolated del(5q)
- MDS, unclassifiable (MDS-U)

Excess blasts
- MDS with excess blasts
  - MDS with excess blasts-1
  - MDS with excess blasts-2

Now will include most cases previously classified as acute erythroid leukemia, based on blast % of total marrow cells
Tug-of-war between genetic and morphologic disease definitions

CML, BCR-ABL1+
AML with inv(16)

MDS
Ph- MPN

Diseases primarily defined by genetic abnormality, despite varied morphologic and clinical presentations

Diseases primarily defined by morphology, despite often strong association with genetic abnormalities

MDS diagnosis should optimally rely on multiple modalities

- Impact of various factors on outcome in 124 MDS patients
- Optimal model was achieved by combining all information
- Future models must also take into account response to various therapies

Gerstung M Nature Comm 2015;6:5901

The ‘gold standard’ for an optimal classification

- Applicable in daily practice
- Reproducible
- Provide prognostic information
- Provide predictive information
  - Identify features that predict better response to Therapy A versus Therapy B
  - Targeted therapies
  - Non-targeted therapies
  - Information still scarce—further study needed to inform future classifications

Conclusions

- New sequencing technologies have paved the way to improve MDS diagnosis
  - Earlier detection
  - More precise risk-stratification
  - Targeted therapies
- As pathologists, we must continually challenge the current diagnostic models as we strive to improve clinical care
  - Incorporate new technologies in diagnosis
  - Test the utility of diagnostic groups in optimally assigning therapy