Overview of System Architecture and Classification Methodologies for MDS and AML

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Contents

1 Introduction

This document outlines our hierarchical diagnostic workflow for haematological disorders. It includes a high-level overview of the classification methodology along with detailed, step-by-step explanations of both Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) classification logic based on the World Health Organization (WHO) 2022 and International Consensus Classification (ICC) 2022 criteria. Furthermore, it provides a preliminary outline for Clonal Haematopoiesis of Indeterminate Potential (CHIP) classification logic, intended for future implementation in Python and integration into our application.

Important Note on Logic Flow

In our classification logic, once a diagnosis is updated from its default value at any step, subsequent steps within that specific classification path (e.g., WHO AML) **will not** trigger a reclassification. This ensures that criteria evaluated earlier in the sequence take precedence over later ones.

Primary guidelines referenced: (WHO 2022; Arber et al. 2022). Concept for CHIP based on sources such as (Jaiswal et al. 2014).

2 Overall Classification Methodology

Our diagnostic workflow employs a hierarchical structure to classify haematological disorders:

1. **AML Classification:**
   - Cases are initially evaluated against the criteria for Acute Myeloid Leukemia.
   - The AML classifier utilizes either WHO 2022 or ICC 2022 guidelines to:
     - Verify key clinical data (e.g., blast cell percentage).
     - Check for characteristic genetic abnormalities.
     - Refine the diagnosis using additional molecular and clinical qualifiers.
2. **MDS Classification:**
   - If AML criteria are not met, the case is assessed for Myelodysplastic Syndrome.
   - MDS classification follows WHO 2022 or ICC 2022 criteria via a stepwise assessment including:
     - Evaluation of TP53 status.
     - Assessment of blast counts and fibrosis levels.
     - Identification of specific mutations (e.g., *SF3B1*).
     - Detection of specific cytogenetic features (e.g., deletion 5q).
     - Examination of morphological markers of dysplasia.

3. **Future CHIP Classification:**
    - Cases not clearly meeting AML or MDS criteria will be evaluated by the planned CHIP classifier.
    - CHIP represents a pre-malignant state characterized by clonal haematopoietic mutations without overt haematological malignancy.

The subsequent sections provide detailed logic for AML and MDS classification.

Methodology based on (WHO 2022; Arber et al. 2022).

3 System Architecture and Workflow

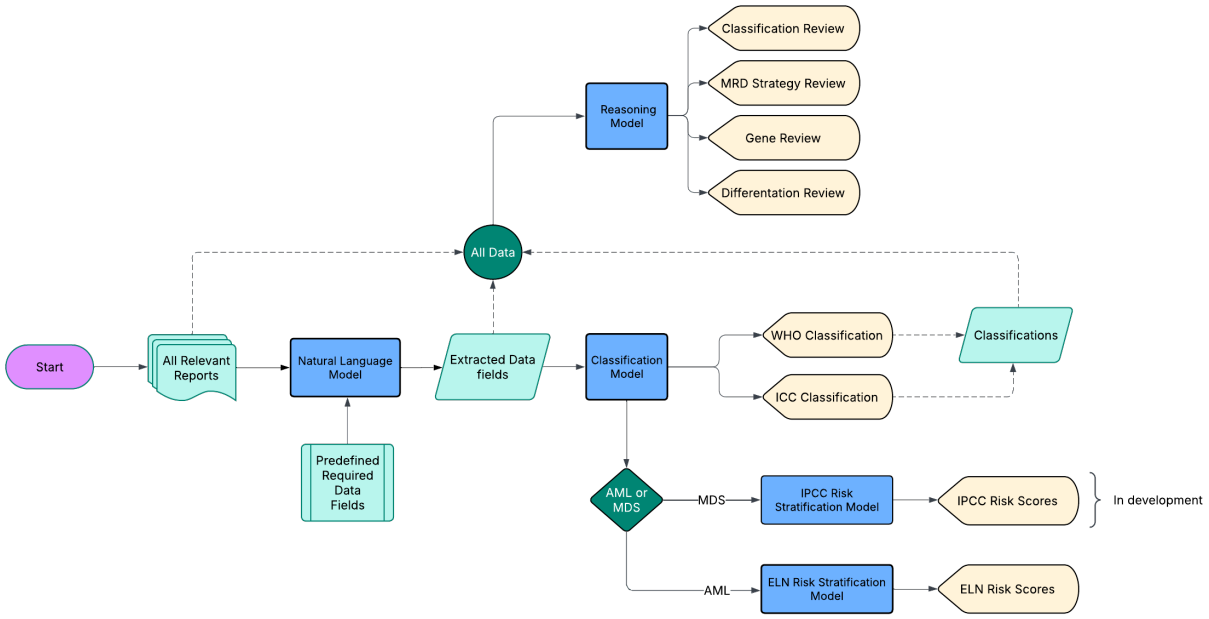

Figure 1: High-level architecture flowchart for the haematological diagnostic system.

Figure 1 illustrates the overall architecture of our diagnostic system. The process is organized into the following major stages:

1. **Data Ingestion:**
    - The diagnostician inputs clinical data, along with molecular and cytogenetic reports, into the designated input areas of the application.
2. **Natural Language Processing (NLP):**
    - A Large Language Model (LLM) processes unstructured text from clinical reports to extract key parameters, such as blast cell percentages, genetic markers, and cytogenetic findings.
3. **Reasoning and Classification:**

- The extracted dataset is passed to a classification module that applies the diagnostic logic.
- This engine utilizes two parallel classification pathways:
  - **WHO 2022 Pathway:** Independently classifies the case using WHO guidelines.
  - **ICC 2022 Pathway:** Independently classifies the case using ICC guidelines.
- Each pathway sequentially evaluates the data, starting with validation of key metrics and then checking for disease-defining abnormalities. The precedence rule (earlier steps override later ones) applies within each pathway.

4. **Risk Stratification:**
   - For cases classified as AML or MDS, specialized risk stratification models (e.g., based on IPSS-M/IPSS-R for MDS, ELN 2022 for AML) are applied to generate risk scores.
   - These scores provide further clinical insights to aid in treatment planning.
5. **Future CHIP Classification:**
   - If the case does not clearly meet AML or MDS criteria, a future module will assess for CHIP.
   - This module will employ an analysis of mutation profiles and variant allele frequencies (VAF) to identify potential CHIP cases.

In summary, the system integrates data extraction, logical reasoning, dual-pathway classification, and risk stratification into a cohesive pipeline. Its modular design allows components to be updated independently as clinical guidelines evolve.

Classification pathways based on (WHO 2022; Arber et al. 2022). Risk stratification concepts draw from (Döhner et al. 2022; Bernard et al. 2022; Greenberg et al. 2012). CHIP concepts based on sources like (Jaiswal et al. 2014).

4 Detailed Explanation of AML Classification Logic

4.1 AML Classification — WHO 2022

Note on WHO 2022 AML Logic

Each subsequent step is applied only if the classification remains at its default value ("Acute Myeloid Leukemia, [to be further defined by differentiation]"). Once a step updates the classification, later checks do not reclassify the case.

Step 1: Validate Blast Percentage

- Verify that the reported percentage of blast cells is available and falls within a valid range (0–100%).
- If the value is missing or invalid, an error is returned, halting this pathway.
- Ensures subsequent classification is based on reliable data.

Step 2: Set Default Classification

- Establish a default diagnosis: "Acute Myeloid Leukemia, [to be further defined by differentiation]".
- Serves as a placeholder until specific genetic or phenotypic features refine the diagnosis.

Step 3: Evaluate AML-Defining Genetic Abnormalities

- Review a predefined mapping of gene/cytogenetic markers associated with WHO 2022 AML-defining recurring genetic abnormalities (e.g., t(8;21) *RUNX1::RUNX1T1*, inv(16) *CBFB::MYH11*, t(15;17) *PML::RARA*, *NPM1* mutation, biallelic *CEBPA* mutation, etc.).
- Identify which of these markers are present.
- For certain markers (e.g., *BCR::ABL1*, *CEBPA* bZIP), the blast percentage must be $\geq 20\%$. For others (e.g., *PML::RARA*, *NPM1*), any blast percentage suffices for AML diagnosis if the marker is present.
- If a defining marker is found meeting its blast criteria, update the classification accordingly (e.g., "AML with *NPM1* mutation").
- If no characteristic markers are found and the blast percentage is $< 20\%$, the case is not classified as AML at this step and may proceed to MDS evaluation later.

Step 4: Assess for Myelodysplasia-Related (MR) Genetic Mutations

- If the diagnosis remains default and blasts $\geq 20\%$, evaluate for mutations typically associated with myelodysplasia (e.g., *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*).
- If one or more such mutations are detected, update the diagnosis to "AML, myelodysplasia-related".

Step 5: Assess for Myelodysplasia-Related (MR) Cytogenetic Abnormalities

- If the diagnosis remains default and blasts $\geq 20\%$, examine cytogenetic data for abnormalities defined as myelodysplasia-related by WHO 2022 (e.g., -7, del(7q), -5, del(5q), i(17q), -17, del(17p), -13, del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13), complex karyotype).
- If such abnormalities are present, update the diagnosis to "AML, myelodysplasia-related".

Step 6: Override Based on Differentiation (AML, NOS)

- If the diagnosis is still default (implying blasts $\geq 20\%$ and no defining genetic or MR features found), use morphological and cytochemical/immunophenotypic information to classify based on differentiation (e.g., AML with minimal differentiation, AML without maturation, AML with maturation, Acute myelomonocytic leukemia, etc.). Update the diagnosis to "AML, not otherwise specified (NOS), [subtype based on differentiation]".
- For example, if differentiation suggests Acute Erythroid Leukemia, update diagnosis.

Step 7: Append Clinical Qualifiers

- Add relevant clinical qualifiers to the diagnosis if applicable:
  - If there is a history of cytotoxic therapy, append "(therapy-related)".
  - If there is a known germline predisposition (excluding certain conditions like Down Syndrome for specific AML subtypes), note this, potentially as "(germline predisposition)".
  - History of prior MDS or MPN might also be noted if relevant to the final classification type.

Finalization (WHO 2022)

- Append the suffix "(WHO 2022)" to the final diagnosis string.
- Return the final diagnosis along with a detailed derivation log explaining the steps taken.

4.2 AML Classification — ICC 2022

Note on ICC 2022 AML Logic

Subsequent steps are applied only if the classification remains at its default value ("AML, NOS"). The blast threshold for ICC AML diagnosis is generally $\geq 10\%$.

Step 1: Validate Blast Percentage

- Verify that the blast percentage is available and valid (0–100%).
- Return an error if data is missing or invalid.

Step 2: Set Default Classification

- Establish a default diagnosis: "AML, NOS".

Step 3: Evaluate AML-Defining Genetic Abnormalities

- Use the ICC-specific list of defining genetic abnormalities (similar but potentially slightly different groupings or names than WHO, e.g., includes AML with *NUP98* rearrangement).
- Check if any defining abnormality is present. Generally, a blast count $\geq 10\%$ is required, but some abnormalities (like t(15;17)) may qualify regardless of blasts.
- If criteria are met, update the diagnosis (e.g., "AML with t(8;21)(q22;q22.1); *RUNX1::RUNX1T1*").

Step 4: Assess for Biallelic *TP53* Inactivation

- If diagnosis is still default and blasts $\geq 10\%$, evaluate for evidence of biallelic *TP53* inactivation (e.g., two distinct mutations, or one mutation plus loss of heterozygosity/copy number loss).
- If detected, update the diagnosis to "AML with mutated *TP53*".

Step 5: Assess for Myelodysplasia-Related Gene Mutations

- If diagnosis remains default and blasts $\geq 10\%$, check for the ICC-defined list of myelodysplasia-related gene mutations (similar to WHO list).
- If present, update the diagnosis to "AML with myelodysplasia-related gene mutation".

Step 6: Assess for Myelodysplasia-Related Cytogenetic Abnormalities

- If diagnosis remains default and blasts $\geq 10\%$, check for ICC-defined myelodysplasia-related cytogenetic abnormalities (similar to WHO list).
- If present, update the diagnosis to "AML with myelodysplasia-related cytogenetic abnormality".

Step 7: Final Blast-Count Check and MDS/AML Category

- If the diagnosis is still "AML, NOS" (meaning blasts $\geq 10\%$ initially but no specific genetic/MR category met):
  - If the final validated blast percentage is $< 10\%$, reclassify as "Not AML, consider MDS classification".
  - If the blast percentage is 10–19%, update the diagnosis to "MDS/AML".
  - If the blast percentage is $\geq 20\%$, the diagnosis remains "AML, NOS". (Differentiation subtypes like WHO are not primary categories in ICC but may be noted descriptively).

Step 8: Append Clinical Qualifiers

- Append additional qualifiers based on clinical context:
  - If therapy-related, append "(therapy-related)".
  - Note germline predisposition if applicable.
  - Note history of MDS/MPN if relevant.

Finalization (ICC 2022)

- Append the suffix "(ICC 2022)" to the final diagnosis.
- Return the final diagnosis along with a detailed derivation log.

Detailed AML logic derived from (WHO 2022; Arber et al. 2022). See also ELN recommendations (Döhner et al. 2022).

5 Detailed Explanation of MDS Classification Logic

5.1 MDS Classification — WHO 2022

Note on WHO 2022 MDS Logic

This pathway is typically entered if AML criteria are not met. Later steps only apply if the classification remains at its default value ("MDS, unclassifiable"). Requires presence of cytopenia(s) and meeting general MDS criteria.

Step 1: Default Classification

- Begin with a default diagnosis: "MDS, unclassifiable". Assumes initial checks for cytopenias and basic MDS features are met.

Step 2: Assess for Biallelic *TP53* Inactivation

- Evaluate for biallelic *TP53* inactivation.
- If present, update the diagnosis to "MDS with biallelic *TP53* inactivation". Finalize with suffix.

Step 3: Evaluate Blast Percentage and Fibrotic Status

- If diagnosis is default, check blast percentage and fibrotic status (bone marrow fibrosis grade MF-2 or MF-3).
  - Check fibrosis first for low blast cases. If blasts $< 5\%$ and fibrosis MF-2/3, classify as "MDS, fibrotic". Update classification if applicable.
  - Then check blasts: If 5–9% (peripheral blood 2–4%) and not already classified as fibrotic, assign "MDS with increased blasts 1 (MDS-IB1)". Update classification if applicable.
  - If blasts 10–19% (peripheral blood 5–19%) and not already classified as fibrotic, assign "MDS with increased blasts 2 (MDS-IB2)". Update classification if applicable.

Step 4: Assess for *SF3B1* Mutation

- If diagnosis remains default (implies blasts $< 5\%$ or blasts 5–9% but no fibrosis), evaluate for *SF3B1* mutation.
- If detected (and meets VAF criteria if specified), update diagnosis to "MDS with low blasts and *SF3B1* mutation (MDS-LB-SF3B1)".

Step 5: Evaluate for Isolated del(5q)

- If diagnosis remains default (blasts $< 5\%$, no *SF3B1*), check for isolated del(5q) cytogenetic abnormality (with specific constraints on other abnormalities).
- If present, update diagnosis to "MDS with low blasts and isolated del(5q) (MDS-LB-5q)".

Step 6: Assess for Hypoplasia

- If diagnosis remains default (blasts $< 5\%$, no *SF3B1*, no isolated del(5q)), assess for bone marrow hypocellularity based on age-adjusted criteria.

- If found, update diagnosis to "MDS, hypoplastic (MDS-h)".

Step 7: Evaluate Dysplastic Lineages (MDS-LB)

- If diagnosis is still default (blasts $< 5\%$, no defining genetic/hypoplastic features), evaluate the number of dysplastic lineages (requires $\geq 10\%$ dysplastic cells in a lineage).
  - If dysplasia present in only one lineage, update to "MDS with low blasts, single lineage dysplasia (MDS-LB-SLD)".
  - If dysplasia present in multiple lineages, update to "MDS with low blasts, multilineage dysplasia (MDS-LB-MLD)".
- If no significant dysplasia is found but other MDS criteria (cytopenias, non-defining clonal marker) are met, it might remain "MDS, unclassifiable" or require further review.

Step 8: Append Clinical Qualifiers

- Append relevant qualifiers (e.g., "(therapy-related)", "(germline predisposition)").

Finalization (WHO 2022)

- Append the suffix "(WHO 2022)" to the final diagnosis.
- Return the diagnosis and derivation log.

5.2 MDS Classification — ICC 2022

Note on ICC 2022 MDS Logic

Applied if AML criteria are not met. Uses a 10% blast threshold for MDS/AML category. Requires cytopenia(s).

Step 1: Default Classification

- Begin with a default diagnosis: "MDS, NOS". Assumes cytopenias are present.

Step 2: Assess for Biallelic *TP53* Inactivation

- Evaluate for biallelic *TP53* inactivation.
- If present (and blasts $< 10\%$), update diagnosis to "MDS with mutated *TP53*". Finalize with suffix. (If blasts $\geq 10\%$, it falls under AML with mutated *TP53*).

Step 3: Evaluate Blast Percentage

- If diagnosis is default, check blast percentage.
  - If blasts 10–19%, update diagnosis to "MDS/AML". Finalize with suffix.
  - If blasts 5–9%, update diagnosis to "MDS with excess blasts (MDS-EB)". Proceed to check genetics.

- If blasts $< 5\%$, proceed to next steps.

Step 4: Assess for *SF3B1* Mutation

- If diagnosis is default or MDS-EB (i.e., blasts $< 10\%$), evaluate for *SF3B1* mutation.
- If detected, update diagnosis to "MDS with mutated *SF3B1*". If it was previously MDS-EB, the *SF3B1* takes precedence. Finalize with suffix.

Step 5: Evaluate for del(5q)

- If diagnosis is default or MDS-EB (blasts $< 10\%$, no *TP53* or *SF3B1*), check for del(5q), isolated or with one other non-chromosome 7 abnormality.
- If present, update diagnosis to "MDS with del(5q)". Finalize with suffix.

Step 6: Evaluate Dysplastic Lineages (MDS, NOS)

- If diagnosis remains default or MDS-EB (blasts $< 10\%$, no defining genetics), assess number of dysplastic lineages.
  - If diagnosis was MDS-EB, keep it as "MDS with excess blasts".
  - If diagnosis was default (blasts $< 5\%$):
    - If single lineage dysplasia, update to "MDS, NOS with single lineage dysplasia".
    - If multilineage dysplasia, update to "MDS, NOS with multilineage dysplasia".
    - If no significant dysplasia but cytopenias + clonal marker present, potentially "MDS, NOS" (final classification depends on overall picture).

Step 7: Evaluate Other Cytogenetic Features (MDS, NOS)

- If diagnosis remains "MDS, NOS" (blasts $< 5\%$, no defining genetics, may or may not have significant dysplasia), check for other cytogenetic abnormalities indicative of MDS (e.g., -7, del(7q), +8, del(20q), complex karyotype) not already used for classification.
- Presence of such features supports the MDS, NOS diagnosis, especially if dysplasia is minimal or absent but cytopenias persist. No specific ICC subcategory is typically assigned here beyond "MDS, NOS".

Step 8: Append Clinical Qualifiers

- Append qualifiers (e.g., "(therapy-related)", "(germline predisposition)").

Finalization (ICC 2022)

- Append the suffix "(ICC 2022)" to the final diagnosis.
- Return the diagnosis and derivation log.

Detailed MDS logic derived from (WHO 2022; Arber et al. 2022). Risk scoring concepts based on (Bernard et al. 2022; Greenberg et al. 2012).

6 Future Integration: CHIP Classification Logic Outline

This section provides a high-level conceptual outline for the Clonal Haematopoiesis of Indeterminate Potential (CHIP) classification logic, which will be developed further.

6.1 CHIP Classification Concept

CHIP is defined by the presence of somatic mutations in haematopoietic stem cells in individuals without unexplained cytopenias, prior myeloid malignancy history, or other specific clonal disorders.

Key Criteria (Conceptual):

- **Mutation Presence:** Detection of one or more somatic mutations in known leukemia-associated genes (e.g., *DNMT3A, TET2, ASXL1, JAK2*, etc.).
- **Variant Allele Frequency (VAF):** The mutation must meet a minimum VAF threshold, typically $\geq 2\%$ for autosomal mutations (or $\geq 4\%$ for X-linked in males).
- **Exclusion Criteria:** The individual must **not** have:
  - Unexplained persistent cytopenias (would point towards CCUS - Clonal Cytopenias of Undetermined Significance, or potentially MDS).
  - A diagnosis of MDS, MPN, AML, or other haematologic malignancy.
  - Other clonal disorders like Paroxysmal Nocturnal Hemoglobinuria (PNH).
  - Reactive or physiological causes for clonal expansion (e.g., recent severe infection, specific therapies).

Proposed Logic Flow (High-Level):

1. **Input Check:** Verify availability of mutation data (gene panel results) and clinical information (CBC, history).
2. **AML/MDS Exclusion:** Confirm the case did not meet criteria for AML or MDS by either WHO or ICC pathways.
3. **Mutation Filter:** Identify somatic mutations in canonical CHIP-associated genes meeting the VAF threshold ($\geq 2\%$).
4. **Cytopenia Check:** Verify the absence of persistent, unexplained cytopenias (using standard thresholds like Hb $<$ 10–11 g/dL, ANC $<$ 1.0–1.5 x10^9/L, Platelets $<$ 100–150 x10^9/L - specific thresholds need definition).
5. **History Check:** Confirm no history of myeloid malignancy or other excluding clonal disorders.
6. **Classification:** If a qualifying mutation is found and exclusion criteria are met, classify as "CHIP". If cytopenias are present, classify as "CCUS" (or flag for potential MDS re-evaluation). If no qualifying mutation, classify as "No clonal haematopoiesis detected".

6.2 Implementation Considerations

- This outline is preliminary and requires detailed definition of gene lists, VAF handling, cytopenia thresholds, and exclusion logic based on evolving guidelines (e.g., potential WHO 2022 or ICC 2022 definitions/mentions of CHIP/CCUS).
- The logic needs to be modular for Python implementation.
- Careful integration is needed to ensure cases are only assessed for CHIP/CCUS if they clearly do not fit AML/MDS categories.

Outline based on established CHIP definitions and criteria, see e.g., (Jaiswal et al. 2014). Evolving definitions in (WHO 2022; Arber et al. 2022) should also be considered.

7 Next Steps Summary

The immediate next steps involve:

- Finalizing the detailed CHIP/CCUS classification logic, aligning with current best practices and guideline interpretations (WHO/ICC).
- Translating the refined CHIP/CCUS logic into Python code for integration into the diagnostic application's classification module.
- Rigorously validating the CHIP/CCUS classifier against clinical datasets and expert review to ensure accuracy and consistency with established definitions.
- Continuously monitoring and updating all classification modules (AML, MDS, CHIP/CCUS) as guidelines evolve.

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