The National Myelodysplastic Syndromes Natural History Study

Sponsored by the National Heart, Lung, and Blood Institute in collaboration with the National Cancer Institute

Study Publications List

1. Gorak E et. al. ***Discordant Pathologic Diagnoses of Myelodysplastic Neoplasms and Their Implications for Registries and Therapies.*** Blood Advances, published August 2023
   - Pathologic diagnosis of MDS can be challenging due to variability in interpretation of morphology and quantification of dysplasia.
   - Misdiagnosis can lead to suboptimal treatment decisions and errors in population-based estimates of MDS incidence and mortality.
   - NHLBI National MDS Natural History Study uniquely supports rigorous comparisons of pathologic diagnoses in a well-characterized cohort.
   - Accurate MDS diagnoses and prognosis depends on strong collaboration between clinicians and skilled pathologists
2. DeZern A. et. al. ***Utility of Targeted Gene Sequencing to Differentiate Myeloid Malignancies from other Cytopenic Conditions.*** Blood Advances, published July 2023
   - Manuscript presents a 2-stage model that successfully predicts development of myeloid malignancy and MDS based only on mutations found in 18 genes
   - Model leverages the wealth of targeted sequencing data available from the MDS cohort
   - Implications are that sequencing data alone may be sufficient to help clinicians delay or even defer a marrow assessment if mutations suggest a low-likelihood of MDS.
   - An online version of the diagnostic tool will be available for research use on the MDS Study website.
3. Abel G.A. et. al. ***Health-Related Quality of Life and Vulnerability among People with Myelodysplastic Syndromes: A US National Study.*** Blood Advances, published July 2023
   - Health-related quality of life (HRQoL) and vulnerability are variably affected in patients with myelodysplastic syndromes (MDS) and other cytopenic states; however, the heterogeneous composition of these diseases has limited our understanding of these domains.
   - For patients in the MDS Natural History Study, HRQoL and vulnerability are variably affected among those with MDS and other cytopenic states, including those at-risk for MDS.
   - For those with MDS, HRQoL was worse for vulnerable participants and those with worse prognosis.
   - Lower-risk MDS was associated with better HRQoL, but this relationship was lost among the vulnerable.
4. Miller C. et. al. ***Failure to Detect Mutations in U2AF1 Due to Changes in the GRCh38 Reference Sequence.*** Journal of Molecular Diagnostics, published January 2022
   - The U2AF1 gene is a core part of mRNA splicing machinery and frequently contains somatic mutations that contribute to oncogenesis in myelodysplastic syndrome, acute myeloid leukemia, and other cancers.

- A change introduced in the GRCh38 version of the human reference build prevents detection of mutations in this gene, and others, by variant calling pipelines.
- This study describes the problem in detail and shows that a modified GRCh38 reference build with unchanged coordinates can be used to ameliorate the issue.

5. Sekeres M.A. et. al. ***The National MDS Natural History Study: design of an integrated data and sample biorepository to promote research studies in myelodysplastic syndromes.*** Leukemia & Lymphoma, published May 2019
   - To facilitate the acquisition and distribution of MDS biospecimens to the wider scientific community and support scientific discovery in this disease, the National MDS Natural History study was initiated by the National Heart, Lung, and Blood Institute (NHLBI) and is being conducted in collaboration with community hospitals and academic medical centers supported by the National Cancer Institute (NCI).
   - This manuscript describes the structure and goals of the study, which will recruit up to 2000 MDS patients or overlapping myeloproliferative neoplasms (MDS/MPN) and up to 500 cases of idiopathic cytopenia of undetermined significance (ICUS).
   - The National MDS Natural History Study (NCT02775383) will offer the world's largest disease-focused tissue biobank linked to longitudinal clinical and molecular data in MDS.
   - Here, we report on the study design features and describe the vanguard phase of 200 cases.
   - The study assembles a comprehensive clinical database, quality of life results, laboratory data, histopathology slides and images, genetic information, hematopoietic and germline tissues representing high-quality biospecimens and data from diverse centers across the United States.
6. Padron E. et. al. ***Germ Line Tissues for Optimal Detection of Somatic Variants in Myelodysplastic Syndromes.*** Blood, published May 2018
   - This prospective study assessed the impact of quantity, quality, and hematopoietic contamination on somatic mutation detection in 4 candidate germ line tissues by using whole exome sequencing (WES) and capture-based targeted resequencing validation.
   - Skin biopsies were contaminated with neoplastic variants, which can result in missed variant identification when using our variant calling approach.
   - Despite the hematopoietic origin of T cells, they yield sufficient DNA and high rates of somatic variant calls when highly purified (>95%).
   - Epithelial cells derived from buccal swabs are suitable controls when procedures to minimize leukocyte contamination are implemented, and buccal swabs are superior to hair follicles because of low DNA quantity per hair.