Universal germline genetic testing in patients with hematologic malignancies using DNA isolated from nail clippings

While identifying hereditary cancer predisposition in individuals with hematologic malignancies (HM) is critical for optimal clinical management,[1-5] genetic testing for these individuals is limited, in part, by the difficulty in obtaining DNA suitable for germline analysis. Peripheral blood, saliva and buccal swabs are often contaminated with malignant cells in patients with HM.[6] Cultured fibroblasts obtained through skin biopsies are used for germline testing of patients with HM, but the invasive nature of the procedure and the multiple week-long culture time before testing can be performed limits the utility of this specimen.

Nail clippings represent a non-invasive source of DNA that can be used for germline testing.[7,8] Here, we describe a novel, clinically validated, and New York State Department of Health-approved next-generation sequencing assay for germline testing of patients with HM using DNA isolated from nail clippings. We describe the institution-wide implementation of this assay, the initial clinical findings in the cohort of patients tested, and the clinical benefit experienced by these patients as a result of the expanded genetic testing.

All patients in the study provided written informed consent for genetic testing under an institutional review board-approved protocol (12-245) as part of the Memorial Sload Kettering - Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT; ClinicalTrials.gov identifier, NCT01775072) paired tumor-blood DNA sequencing test.

Genomic DNA was isolated from peripheral blood, saliva, and fresh-frozen, paraffin-embedded tissues as described previously.[9,10] For DNA isolation from nail clippings, ten fingernails or ten toenails were collected from the patient and submitted to the laboratory as long thin strands in a dry sterile container. Of these fingernail or toenail clippings, 20 mg (~3 thin slivers) were pulverized using a BeadBlaster 24 instrument (Benchmark Scientific, NJ, USA). Samples were lysed by heating at 56°C and collected using a QIAamp DNA investigator kit (Qiagen, Valencia, CA, USA). DNA samples were normalized to yield up to 250 ng input and maximized to 55 μL in TE Buffer. The median genomic DNA yield in 505 samples that were extracted was 569 ng. Extracted genomic DNA was sheared using a Covaris E200 instrument (Covaris, Woburn, MA, USA) and libraries were prepared as described previously.[9,10] Briefly, sequence libraries were prepared using the KAPA HTP protocol (Kapa Biosystems, Wilmington, MA, USA) and Biomek FX system (Beckman Coulter, Brea, CA, USA) through a series of enzymatic steps including shearing of double-stranded DNA, end repair, A-base addition, ligation of dual-barcoded sequence adaptors, and low-cycle polymerase chain reaction amplification. Multiple barcoded sequence libraries were pooled and captured using our custom-designed biotinylated probes (Integrated DNA Technologies, Coralville, IA, USA). Analysis of 505 nail samples showed that 1% (5/505) of the samples had a coverage (read depth) <150X, the minimum threshold for this assay, and were considered insufficient for germline analysis. Variant calling, annotation, and interpretation were performed as described previously.[9-11] Briefly, variants called using the MuTect and Genome Analysis Toolkit (GATK) Haplotypecaller were filtered based on 25% variant allele fraction for single nucleotide variants (SNV) and 15% for insertions/deletions (indels) together with 20X coverage thresholds. Copy number variants (CNV) (deletions and duplications of single or multiple exons) in the target genes were captured and assessed using a validated pipeline developed in-house.

To evaluate first whether nails could provide a source of DNA suitable for germline testing, the variant allele fraction of 2,398 somatic variants in 82 cancer susceptibility genes (Germline MSK-IMPACT-Heme, *Online Supplementary Table S1*) were interrogated in the nails from 2,611 patients who underwent MSK-IMPACT-Heme (MSK-IMPACT for hematologic malignancies).[11] Seven (0.29%) of 2,398 somatic variants were found to have a variant allele frequency >20% in the nails (N=1 for *CALR, CHEK2, MPL, PMS2*, and *RUNX1* and N=2 for *ETV6*), six of which were from one patient with a myeloproliferative neoplasm and fibrotic bone marrow, while the remaining variant was in a patient with myelodysplastic syndrome, suggesting that caution may be warranted when performing germline testing using nail DNA in patients with a fibrotic bone marrow in the absence of a matched tumor. Therefore, only 2/2,611 (0.08%) patients tested had somatic contamination in the nails that could potentially confound germline analysis in the absence of a matched tumor, and in 99.92% of cases, nail DNA was deemed suitable for germline testing.

For validation of Germline MSK-IMPACT-Heme as a genetic testing assay, its performance was compared to that of the clinically validated panel MSK-IMPACT[9] (used for germline testing in patients with solid tumors) for 68 genes shared by the two assays. Coverage (read depth at each target position) and variant calling were analyzed in blood specimens from 21 individuals run on MSK-IMPACT and compared to those of specimens from the same individuals (nail clippings [N=14], saliva [N=11], and/or blood [N=19]) run on Germline MSK-IMPACT-Heme. Each target exon and adjacent splice sites (±20 bp) had equivalent coverage. There was 100%

concordance in variant calling using Germline MSK-IMPACT-Heme and MSK-IMPACT for 1,482 variants (1,355 SNV), 109 insertion/deletions (indels), and 18 large deletions and insertions (CNV), including variants with a range of clinical significance classifications (Figure 1A-C).

The clinical testing cohort consisted of 240 consecutive patients, unselected based on current genetic testing criteria, prospectively consented to germline analysis by their treating physicians as part of MSK-IMPACT-Heme between June 2022 and July 2023 (*Online Supplementary Table S2*), 210 of whom had a diagnosis of a HM (or aplastic anemia) and 30 individuals who underwent testing as part of an evaluation for possible HM. Individuals who had previously undergone allogeneic stem cell transplantation were excluded. Nail samples were used for individuals with myeloid and T-cell malignancies (212/240; 88%), and for individuals with B-cell lymphomas, saliva samples were also acceptable for germline testing. The most common diagnoses of patients with HM were mature B-cell neoplasms (N=48), myeloproliferative neoplasms (N=42), acute myeloid leukemia (N=35), myelodysplastic syndromes (N=23), and B-lymphoblastic leukemia/lymphoma (N=15) (*Online Supplementary Figure S1*). Nail specimens were used for 212 individuals and saliva specimens were used for 28 individuals. Of the 240 individuals, 38 (15.8%) had pediatric-onset (<18 years old) and 202 (84.2%) had adult-onset disease (*Online Supplementary Table S2*). The median turnaround time from sample accessioning to report sign-out was 10 working days.

Germline pathogenic and likely pathogenic variants (gPV) in hereditary cancer predisposition genes were identified in 17.1% (41/240) of individuals and in 16.7% (35/210) of the patients with a diagnosis of a HM (Table 1, *Online Supplementary Figure S1*). Six of 41 (14.6%) patients with gPV had exon-level deletions. The positivity rate was 17.3% (35/202) in adult patients and 15.8% (6/38) in pediatric patients. Among the patients with a clinical diagnosis of HM, the highest rate of gPV was in those with a myeloproliferative neoplasm (11/42; 26.2%), followed by B-lymphoblastic leukemia/lymphoma (3/15; 20%) (*Online Supplementary Figure S1*).

Eight of 240 (3.3%) patients had gPV in high penetrance genes known to be associated with predisposition to HM. Three individuals in our cohort (3/240; 1.3%) had biallelic variants in genes associated with rare autosomal recessive syndromes (Figure 2) which were all confirmed to be *in trans* by parental testing. The first patient (Figure 2A) had a history of cytopenias and was diagnosed at the age of 25 years with a myelodysplastic syndrome that progressed to myelodysplasia-related acute myeloid leukemia (Figure 2A, middle panel). Germline MSK-IMPACT-Heme revealed two *FANCA* gPV, leading to a diagnosis of Fanconi anemia. A chromosomal breakage study with diepoxybutane on cultured fibroblasts was positive, consistent with Fanconi anemia, and the patient underwent reduced intensity conditioning for treatment of his acute myeloid leukemia. The second patient (Figure 2B) was diagnosed with ataxia telangiectasia at the age of 4 years after presenting with neurological symptoms. At the age of 13 years, the patient developed diffuse large B-cell lymphoma. Previous genetic testing had identified a single *ATM* pathogenic variant (c.8103_8104delAA [p.Ile2702Argfs*15]). Germline MSK-IMPACT-Heme identified this variant and a second pathogenic deletion of *ATM* exons 62-63. The third patient (Figure 2C) developed a large mediastinal mass at the age of 12 years, which was diagnosed as T-cell lymphoblastic leukemia/lymphoma. Germline MSK-IMPACT-Heme identified two *MSH6* gPV, and the patient was diagnosed with constitutional mismatch repair deficiency. Subsequent colonoscopy revealed multiple polyps. Both parents were found to have Lynch syndrome.

Five patients had gPV in autosomal dominant, high penetrance genes associated with predisposition to HM: two with *DDX41*, one each with *ETV6*, *RUNX1*, and *POT1*. The patient with an *ETV6* gPV (Figure 2D) had thrombocytopenia with onset in her 30s and was diagnosed with chronic myelomonocytic leukemia at the age of 59 years. The variant segregated in the patient's daughter, who had thrombocytopenia. A pathogenic *RUNX1* multi-exon deletion was identified in a patient with a previous diagnosis of idiopathic thrombocytopenia purpura, who developed mixed phenotype acute leukemia and simultaneously uterine leiomyosarcoma at the age of 47 years (Figure 2E). The patient with a *DDX41* p.Gln306* gPV was diagnosed with acute myeloid leukemia at the age of 56 years and had a second somatic *DDX41* oncogenic variant (p.Arg525His) identified in the matched bone marrow specimen (Figure 2F). The patient with a *POT1* p.Ile78Thr variant had a history of papillary thyroid carcinoma at the age of 34 years, *JAK2* p.Val617Phe-positive polycythemia vera diagnosed when he was 32 years old, and multiple small papillary renal cell carcinomas diagnosed at 44 years of age, consistent with descriptions of the *POT1* phenotype.[12] Additionally, 20% (6/30) of individuals tested because of a suspicion of a HM were also found to carry gPV (Table 1). Further studies on the benefit of genetic testing in individuals with hematologic abnormalities but no cancer diagnosis may be warranted.

The majority of individuals with gPV (23/41; 56.1%) had variants in homologous recombination pathway genes not currently known to predispose to HM (*CHEK2* [N=7], *BRCA1* [N=5], *ATM* [N=5], *BRCA2* [N=2], *PALB2* [N=2], *FANCA* [N=1], and *FANCC* [N=1]). While variants in these genes have been reported in patients with HM,[13,14] larger cohorts of patients with different tumor types are required to determine whether they confer an increased risk of these cancer types. Additionally, a 28-year-old patient with chronic lymphocytic leukemia had an *MSH6* variant leading to a diagnosis of Lynch syndrome, a 56-year-old patient with chronic lymphocytic leukemia/small lymphocytic lymphoma had an *SDHB* variant and was recently diagnosed with renal cell carcinoma and paraganglioma, and two patients without known personal or family history of schwannoma had *LZTR1* variants associated with schwannomatosis. These results suggest that expanded genetic testing approaches in individuals with HM are likely

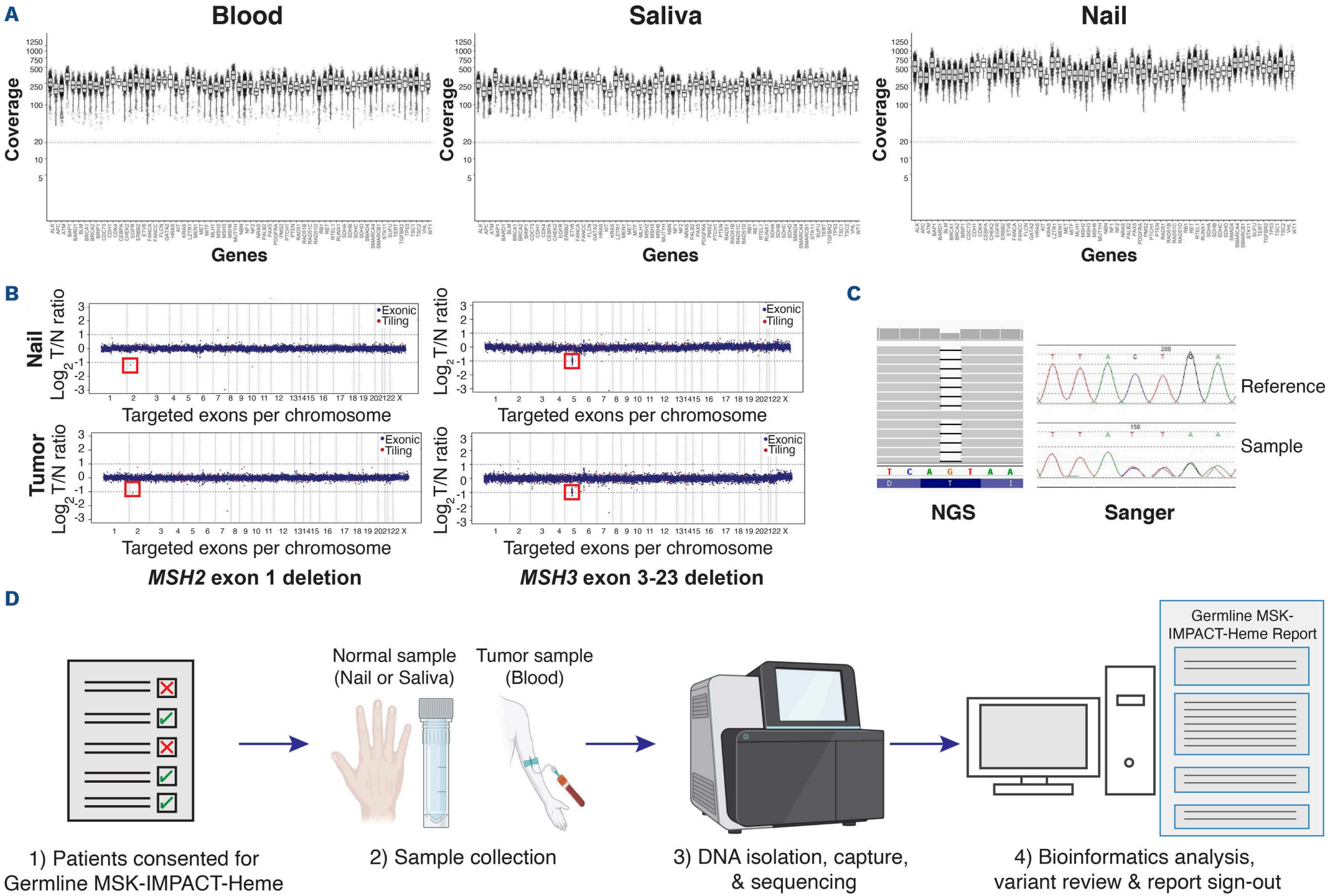

Figure 1. Validation of the Germline MSK-IMPACT-Heme panel and overview of the MSK-IMPACT-Heme workflow. (A) Each target exon and adjacent splice sites (±20 bp) of 68 genes that were common between MSK-IMPACT-Heme and MSK-IMPACT had sufficient (>20X) and equivalent coverage in tested blood, saliva, and nail specimens. (B) Representative copy number plots demonstrating the detection of a single exon (*MSH2* exon 1) deletion and an intragenic multi-exon (*MSH3* exon 3-23) deletion in validation of copy number variant calling using DNA isolated from nail specimens by Germline MSK-IMPACT-Heme. (C) Representative detection of a small deletion (*CHEK2* c.1100delC) variant by the Germline MSK-IMPACT-Heme next-generation sequencing panel and Sanger sequencing using DNA isolated from nail specimens. (D) Overview of the MSK-IMPACT-Heme workflow. Patients referred by their clinical providers are consented for paired tumor-normal sequencing and germline analysis. A sample for a source of normal DNA (nail or saliva) and a sample for a source of tumor DNA (blood, bone marrow, lymph node, or other tissue) are collected. DNA is extracted from the samples, sequence libraries are prepared and captured using MSK-IMPACT-Heme probes. Sequencing is performed and data are analyzed through a custom bioinformatics pipeline to detect and annotate variants. Results are interpreted, classified, and reported by clinical molecular geneticists and molecular pathologists. Reports are transferred to the patient's electronic medical records. Figure 1D was created partly with BioRender.com. T/N: target to normal; NGS: next-generation sequencing.

Table 1. Summary of patients with germline pathogenic/likely pathogenic variants in hereditary cancer predisposition genes.

Age at HM Dx in years	Sex	Clinical Dx	Disease group	Pathogenic variants#	Other malignancy (age at Dx in years)
62	M	MZL	MBN	*APC* c.3920T>A (p.Ile1307Lys), P	No
27	F	ET	MPN	*APC* c.3920T>A (p.Ile1307Lys), P	No
27	M	MPN	MPN	*APC* c.3920T>A (p.Ile1307Lys), P	No
28	M	CLL/SLL	MBN	*APC* c.3920T>A (p.Ile1307Lys), P *MSH6* c.3226C>T (p.Arg1076Cys), LP	No
65	F	MCL	MBN	*ATM* c.2192dupA (p.Tyr731*), P *BLM* exons 6-12 deletion, LP	BC (41); RCC (46)
70	F	CML	MPN	*ATM* c.7271T>G (p.Val2424Gly), P	CEAD (37); ANSC (50); TC (52)
60	M	CML	MPN	*ATM* c.8103_8104delAA (p.Ile2702Argfs*15), P	Melanoma (56)
40	F	MPN	MPN	*ATM* c.901+1G>A, P	No
13	M	DLBCL	MBN	*ATM* exons 62-63 deletion, P *ATM* c.8103_8104delAA (p.Ile2702Argfs*15), P	No
60	M	Myelofibrosis	MPN	*BLM* exons 13-14 deletion, P	No
23	F	B-cell lymphoma	MBN	*BRCA1* c.2635G>T (p.Glu879*), P	No
50	F	Cytopenia	MDS Workup	*BRCA1* c.2800C>T (p.Gln934*), P	HGSOC (47)
64	F	AML	AML	*BRCA1* c.4327C>T (p.Arg1443*), P	BC (41)
40	M	MPN	MPN	*BRCA1* c.68_69delAG (p.Glu23Valfs*17), P	No
49	F	B-cell leukemia	BLL	*BRCA1* exons 7-8 deletion, P	No
54	F	CML	MPN	*BRCA2* c.4276dupA (p.Thr1426Asnfs*12), P	BC, TC
77	M	Cytopenia	MDS Workup	*BRCA2* c.5073dupA (p.Trp1692Metfs*3), P	PC (68)
1	M	MPAL	ALAL	*CHEK2* c.1100delC (p.Thr367Metfs*15), P	No
45	M	AML	AML	*CHEK2* c.1100delC (p.Thr367Metfs*15), P	(Male) BC (62)
46	F	MDS/MPN	MDS	*CHEK2* c.1283C>T (p.Ser428Phe), P	No
16	F	HL	HL	*CHEK2* c.1421G>A (p.Arg474His), LP	No
62	M	AML	AML	*CHEK2* c.444+1G>A, P	No
23	F	ET	MPN	*CHEK2* c.470T>C (p.Ile157Thr), P	No
51	M	MDS/MPN	MDS/MPN	*MUTYH* c.1187G>A (p.Gly396Asp), P	No
33	M	Stem cell donor	MDS Workup	*DDX41* c.415_418dupGATG (p.Asp140Glyfs*2), P	No
56	F	AML	AML	*DDX41* c.916C>T (p.Gln306*), P	No
59	F	CMML	MDS/MPN	*ETV6* c.1196G>A (p.Arg399His), LP	No
25	M	MDS	MDS	*FANCA* exons 18-22 deletion, P *FANCA* c.367C>T (p.Gln123*), P	No
62	F	Lymphadenopathy	MPN Workup	*FANCC* c.456+4A>T, P	No
37	F	DLBCL	MBN	*LZTR1* c.2062C>T (p.Arg688Cys), LP	No
31	F	MPN	MPN	*LZTR1* c.2407delG (p.Val803Serfs*10), LP	No
58	F	Cytopenia	MDS Workup	*MPL* c.1653+1delG, P	PNET (54)
20	M	AML	AML	*MSH3* c.1625dupT (p.Leu542Phefs*12), LP	No

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Age at HM Dx in years	Sex	Clinical Dx	Disease group	Pathogenic variants[#]	Other malignancy (age at Dx in years)
12	M	TCL	MTNN	*MSH6* c.3261dupC (p.Phe1088Leufs*5), P *MSH6* c.3724_3726delCGT (p.Arg1242del), LP	No
66	F	CH	MDS Workup	*MUTYH* c.1187G>A (p.Gly396Asp), P	BC (62)
0	F	BLL	BLL	*PALB2* c.3323delA (p.Tyr1108Serfs*16), P	No
53	M	CLL/SLL	MBN	*PALB2* c.509_510delGA (p.Arg170Ilefs*14), P	No
32	M	PV	MPN	*POT1* c.233T>C (p.Ile78Thr), LP	TC (34); RCC (44)
47	F	MPAL	ALAL	*RUNX1* exons 3-9 deletion, P	ULMS (47)
56	M	CLL/SLL	MBN	*SDHB* c.642+2T>G, LP	PGNG (56); RCC (56)
5	M	BLL	BLL	*TYK2* c.691C>T (p.Arg231Trp), LP	No

[#]Pathogenic (P) and likely pathogenic (LP). HM: hematologic malignancy; Dx: diagnosis; M: male; MZL: marginal zone lymphoma; MBN: mature B-cell neoplasms; F: female; ET: essential thrombocythemia; MPN: myeloproliferative neoplasm; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; MCL: mantle cell lymphoma; BC: breast cancer; RCC: renal cell carcinoma; CML: chronic myeloid leukemia; CEAD: cervical cancer; ANSC: anal squamous cell carcinoma; TC: thyroid cancer; DLBCL: diffuse large B-cell lymphoma; MDS: myelodysplastic syndrome; HGSOC: high-grade serous ovarian cancer; AML: acute myeloid leukemia; BLL: B-lymphoblastic leukemia/lymphoma; PC: prostate cancer; MPAL: mixed phenotype acute leukemia; ALAL: acute leukemia of ambiguous lineage; CMML: chronic myelomonocytic leukemia; HL: Hodgkin lymphoma; PNET: pancreatic neuroendocrine tumor; TCL: T-cell leukemia; MTNN: mature T and NK neoplasms; CH: clonal hematopoiesis; PV: polycythemia vera; ULMS: uterine leiomyosarcoma; PGNG: paraganglioma.

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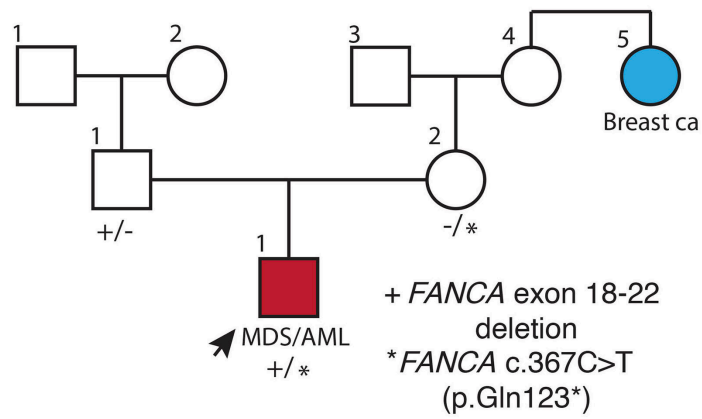

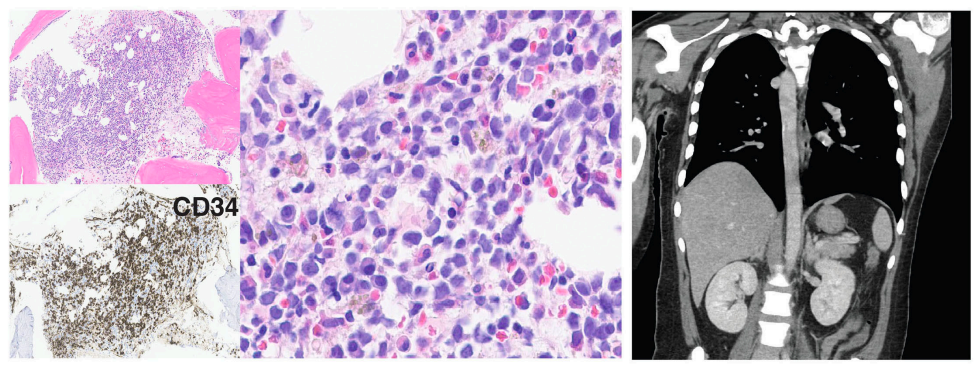

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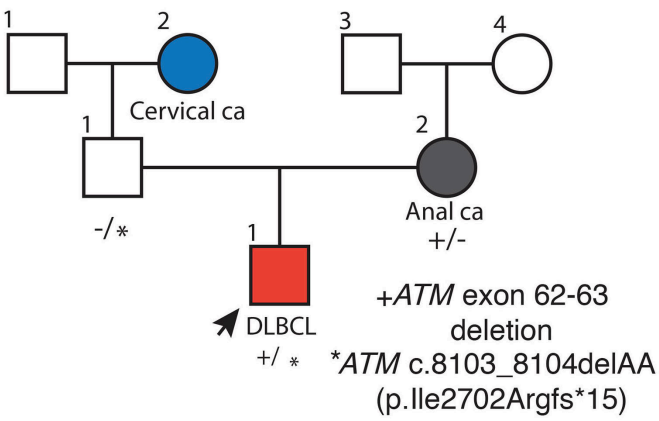

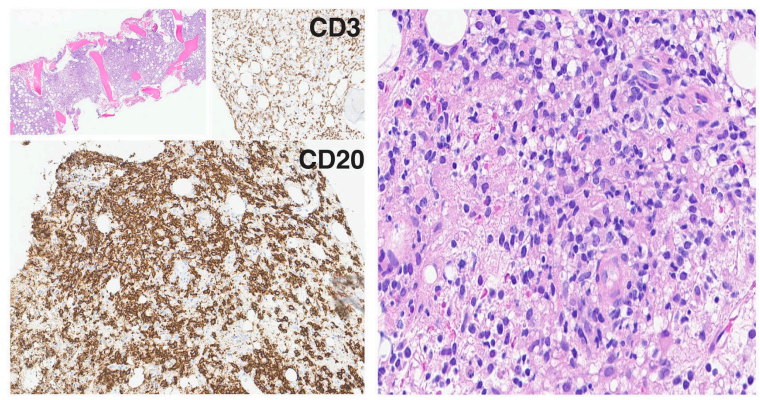

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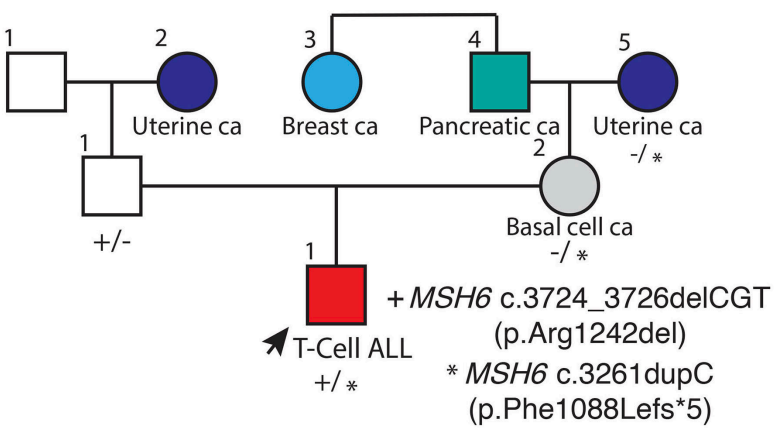

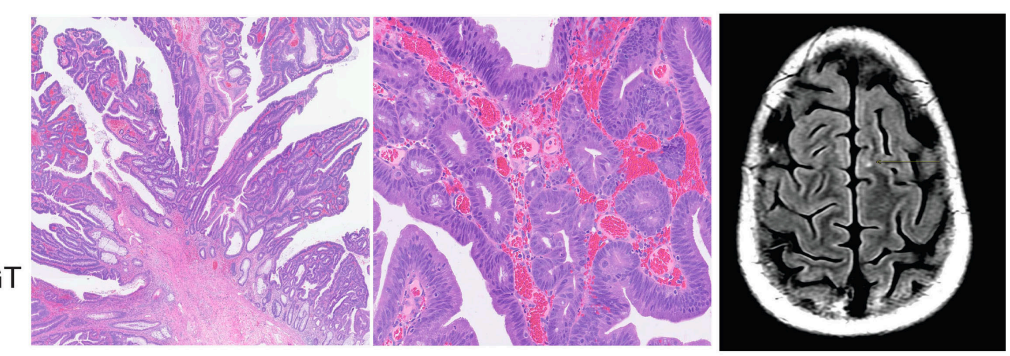

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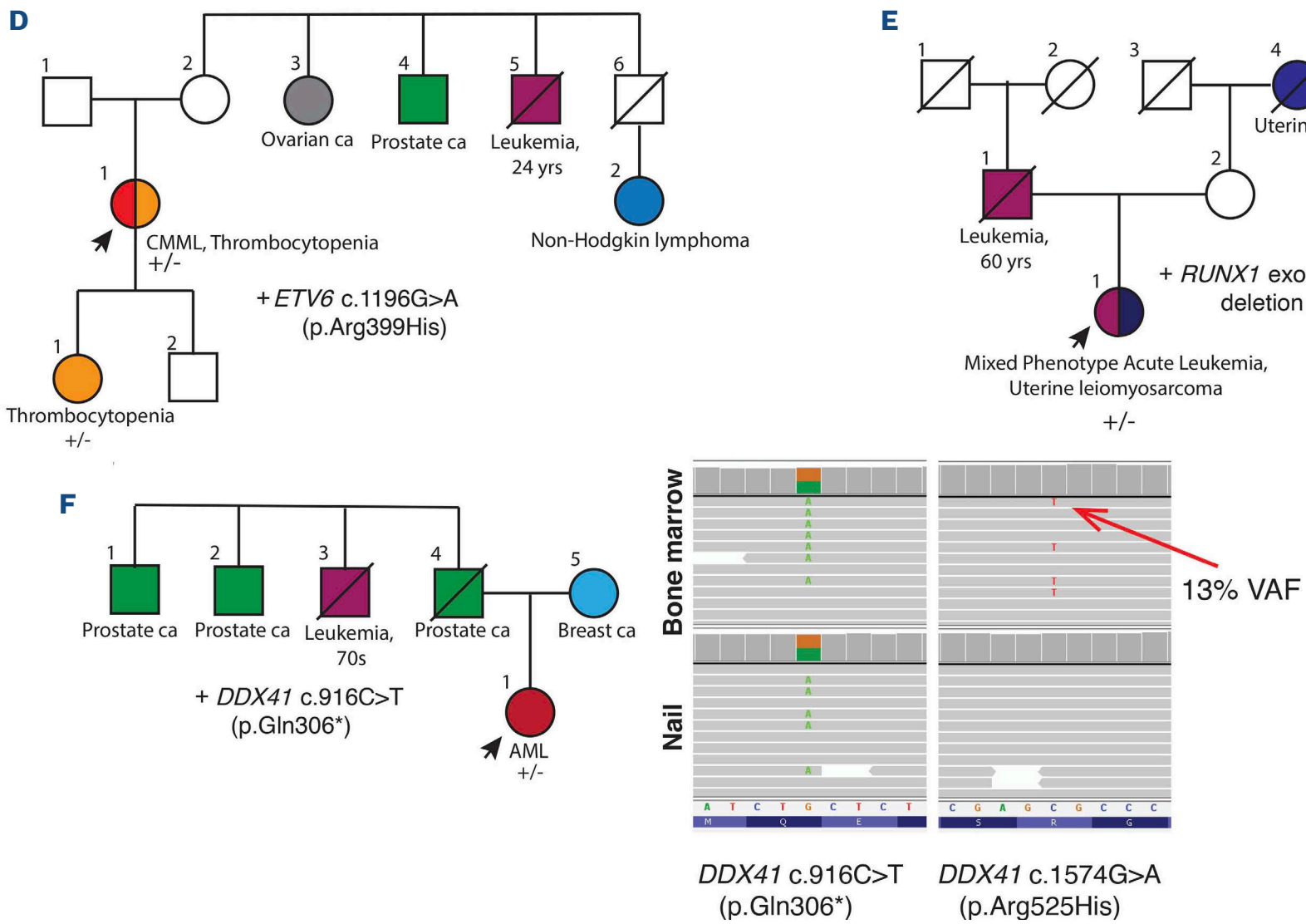

Figure 2. Patients with germline pathogenic/likely pathogenic variants in genes associated with a predisposition to hematologic malignancies. (A) Patient with biallelic germline pathogenic/likely pathogenic variants (gPV) in *FANCA* diagnosed with Fanconi anemia. Left. Pedigree of the patient with biallelic *FANCA* gPV. Middle. A representative core biopsy involved by myelodysplasia-related acute myeloid leukemia (hematoxylin & eosin [H&E], 10X original magnification) with hypercellularity, decreased maturing trilineage hematopoiesis, and increased numbers of blasts in clusters (H&E, 40X original magnification) accounting for 50% of cellularity (highlighted by CD34 immunohistology, 10X original magnification). A right-sided aortic arch was identified in the patient. (B) Patient with biallelic gPV in *ATM* diagnosed with ataxia telangiectasia. Left. Pedigree of the patient with biallelic ATM gPV. Right. A bone marrow biopsy revealed hypercellular marrow (H&E, 4X original magnification) extensively involved by an atypical lymphoid infiltrate (H&E, 4X original magnification) with large-size neoplastic mature B cells (H&E, 40X original magnification and CD20 immunohistology 20X original magnification) and a background of numerous reactive T cells (CD3 immunohistology 20X original magnification), overall consistent with diffuse large B-cell lymphoma. (C) Patient with biallelic gPV in *MSH6* diagnosed with congenital mismatch repair deficiency. Left. Pedigree of the patient with biallelic *MSH6* gPV. Middle. Colonoscopy 4 months after the initial presentation revealed several colonic polyps, including hyperplastic, tubular adenomas, and a tubulovillous adenoma (H&E, 2X original magnification) with villous architecture and columnar cells showing focal high-grade dysplasia (H&E, 20X original magnification). Right. Brain magnetic resonance imaging of the patient showing nonspecific hyperintensities. (D) Pedigree of the patient with *ETV6* gPV. The *ETV6* gPV was identified in the patient with a history of chronic myelomonocytic leukemia and thrombocytopenia and segregated in her daughter with a history of thrombocytopenia. (E) Pedigree of the patient with *RUNX1* gPV. (F) Left. Pedigree of the patient with a *DDX41* c.916C>T (p.Gln306*) gPV. Right. Using next-generation sequencing a germline *DDX41* c.916C>T (p.Gln306*) variant was detected in the patient's nail and bone marrow DNA and a somatic *DDX41* c.1574G>A (p.Arg574His) variant was detected in her bone marrow DNA sample at a variant allele fraction of 13% (right panel). ca: cancer; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; DLBCL: diffuse large B-cell lymphoma; ALL: acute lymphoblastic leukemia; yrs: years; CMML: chronic myelomonocytic leukemia; VAF: variant allele fraction.

to identify hereditary predisposition to a broad spectrum of cancer susceptibility syndromes.

In this report, we describe the development of a novel, high-throughput, germline testing assay for individuals with HM using nail DNA. Currently, DNA from cultured fibroblasts obtained through skin biopsies is the most commonly used type of specimen for germline testing in patients with active HM, although the invasive nature of the procedure and the multiple week-long culture time make it challenging to utilize on a large scale and deliver results in a timely fashion. In a recent study, the median turnaround time for fibroblast culture alone was 28 days and 5% of skin biopsies failed to culture, resulting in the need for an additional biopsy.[15] The median turnaround time of 10 working days for our test was substantially shorter than the amount of time needed for a fibroblast culture and testing time in a typical skin biopsy test. Our rapid and noninvasive germline testing approach allows for an institution-wide initiative towards universal

genetic testing for patients with HM. Remarkably, in the first 240 consecutive patients with HM who consented to genetic testing, a similar proportion tested positive for hereditary cancer susceptibility (17.1%) as in our patients with solid tumors (16.7%) tested under the same institutional review board-approved protocol.[16] Even in this initial cohort, germline findings resulted in therapeutic considerations, initiation of surveillance for additional malignancies, and identification of at-risk relatives.

One limitation of this study is that the panel used does not contain all genes associated with predisposition to HM, for example bone marrow failure and immunodeficiency syndromes. Inclusion in this study required referral by the treating physicians and the patients' consent; therefore, under or over-representation of some predisposed patients cannot be ruled out. Additionally, a prior allogeneic stem cell transplant was one of the exclusion criteria, as a recent study showed that 22% of nail specimens in these individuals had some level of chimerism, with graft-*versus*-host disease being a risk factor for this chimerism.[17] However, if nail DNA can be compared to a pre-transplant host specimen by chimerism analysis using short tandem repeats or similar methodology, and the nail DNA is found to be free of donor contamination, it would be suitable for germline analysis. Despite its limitations, our study shows the feasibility of large-scale genetic testing for individuals with HM using DNA derived from nail clippings. This advance will both allow for larger scale genetic testing studies to help determine which patients with HM are most likely to benefit from routine genetic testing and provide an opportunity to improve the availability and efficiency of clinical germline testing for individuals with HM in the future.

Authors

Ozge Ceyhan-Birsoy,[1*] Elise Fiala,[2,3*] Satshil Rana,[1] Margaret Sheehan,[2] Jennifer Kennedy,[2] Zarina Yelskaya,[1] Vikas Rai,[1] Yirong Li,[1] Ciyu Yang,[1] Donna Wong,[1] Ivelise Rijo,[1] Jacklyn Casanova,[1] Joshua Somar,[1] Nikita Mehta,[1] Hyeonjin Park,[1] Silvana Ostafi,[1] Kanika Arora,[1] Angelika Padunan,[2] Mark D. Ewalt,[1] Umut Aypar,[1] Panieh Terraf,[1] Maksym Misyura,[1] Sofia Haque,[4] Gerald G. Behr,[4] Tamanna Haque,[2] Maria Sulis,[2,3] Mark B. Geyer,[2] Christopher Forlenza,[2,3] Meghan C. Thompson,[2] Maria Carlo,[2] Alicia Latham,[2] Ying Liu,[2] Ahmet Zehir,[1] Rose Brannon,[1] Michael Berger,[1] Luis A. Diaz Jr,[2] Ahmet Dogan,[1] Marc Ladanyi,[1] Kseniya Petrova-Drus,[1] Khedoudja Nafa,[1] Kenneth Offit,[2] Maria Arcila,[1] Zsofia K. Stadler,[2#] Michael F. Walsh[2,3#] and Diana Mandelker[1#]

[1]Department of Pathology and Laboratory Medicine; [2]Department of Medicine; [3]Department of Pediatrics and [4]Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[*]OC-B and EF contributed equally as first authors.

[#]ZKS, MFW, and DM contributed equally as senior authors.

Correspondence:
D. MANDELKER - mandelkd@mskcc.org
M.F. WALSH - walshm2@mskcc.org
Z.K. STADLER - stadlerz@mskcc.org

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Disclosures

MB declares having received consulting fees from AstraZeneca, Eli Lilly, and Paige.AI unrelated to this work and having intellectual property rights with SOPHiA GENETICS related to MSK-IMPACT. ZKS declares that an immediate family member serves as a consultant in Ophthalmology for Adverum, Genentech, Neurogene, Novartis, Optos Plc, Outlook Therapeutics, and Regeneron outside the submitted work. ZKS serves as an Associate Editor for JCO Precision Oncology and as a Section Editor for UpToDate. MCT declares research funding (to the institution) from AstraZeneca, Beigene, Nurix Therapeutics, Genentech, AbbVie, and Genmab, consulting/advisory board services for AstraZeneca, Beigene, Janssen, Pharmacyclics, and LOXO Oncology at Lilly; honoraria from Philips Group Oncology Communications, VJHemOnc, Curio Science LLC, Dava Oncology, Brazilian Association of Hemotherapy and Cellular Therapy (ABHH), MJH Life Sciences, Massachusetts Medical Society, and Peerview; and travel support from Nurix Therapeutics and Dava Oncology. AZ is currently employed at AstraZeneca. DM declares consulting fees from AstraZeneca unrelated to this work. All other authors have no conflicts of interest to disclose.

Contributions

OC-B, EF, ZKS, MFW, and DM conceived and designed the study. All authors acquired data. OC-B, EF, SR, KP-D, MA, ZS, MFW, and DM analyzed and interpreted the data. OC-B, EF, ZS, MFW, and DM wrote the manuscript. All the authors reviewed and approved the manuscript.

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Data-sharing statement

All de-identified genomic results for the patients in this study are available in the cBioPortal for Cancer Genomics at http://cbioportal.org/msk-impact.

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