What To Tell Your Patient With Clonal Hematopoiesis And Why: Insights From Two Specialized Clinics

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Abstract

Acquired genetic mutations in hematopoietic stem or progenitor cells can lead to clonal expansion and imbalanced blood cell production. Clonal hematopoiesis is exceptionally common with human aging, confers a risk of evolution to overt hematologic malignancy, and also increases all-cause mortality and the risk of cardiovascular disease. The degree of risk depends on the specific mutation, number of mutations, mutant allele burden, and concomitant non-genetic risk factors (e.g., hypertension or cigarette smoking). People with clonal hematopoiesis may come to clinical attention in a variety of ways, including during the evaluation of a possible hematologic malignancy, as an incidental discovery during molecular analysis of a non-hematological neoplasm, after hematopoietic cell transplant, or as a result of germline testing for inherited variants. Even though the risk of clonal progression or a cardiovascular event in an individual patient may be low, the possibility of future clinical consequences may contribute to uncertainty and worry, since it is not yet known how to modify these risks. This review summarizes clinical considerations for patients with clonal hematopoiesis, including important points for hematologists to consider discussing with affected persons - individuals who may understandably be anxious about having a mutation in their blood that predisposes them to develop malignancy, but which is statistically more likely to result in a myocardial infarction or stroke. The increasing frequency with which people with clonal hematopoiesis are discovered and the need for counseling these patients is driving many institutions to create specialized clinics; we describe our own experience with forming such clinics.

Introduction

Clonal hematopoiesis, defined by an outsized contribution to circulating blood cell production by a single genetically altered hematopoietic clone in the absence of diagnostic evidence for a hematological neoplasm, is a common biological state in middle-aged and older persons.[1-4] Clonal hematopoiesis usually results from acquisition by a hematopoietic stem or progenitor cell of one or more of a limited repertoire of somatic mutations, although somatic mosaicism and imbalanced hematopoiesis can also result from large structural chromosomal rearrangements.[5,6] Aging-associated clonal hematopoiesis is a risk factor for further mutation acquisition and clonal evolution to an overt hematological neoplasm (Table 1), with a particular increase in the relative risk for developing a myeloid malignancy, as well as for all-cause mortality and specifically death from a cardiovascular event (e.g., myocardial infarction, cerebrovascular accident).[1,7]

When a somatic mutation leading to clonal expansion occurs in a leukemia-associated gene, and the variant allele frequency (VAF, i.e., proportion of mutant DNA) of that mutation is at least ~2% (i.e., more than 4% of circulating blood cells are derived from a single clone, if assuming heterozygosity and diploid state), the term "clonal hematopoiesis of indeterminant potential" (CHIP) can be used.[8,9] The term "CHIP" indicates that the consequence of clonal hematopoiesis for the individual is unknown: such clones usually have no clinical consequence, but they do have the *potential* to further expand or to evolve to overt neoplasia. Alternatively, a clone can contribute to a vascular event by a pro-inflammatory and pro-atherogeneic interaction with endothelium[7,10-12], can worsen heart failure by altering myocardial remodeling[13], or can potentiate other non-neoplastic pathology.[14,15]

CHIP is present in at least 10-20% of people by age 70 years.[2,3] Smaller expanded hematopoietic clones not meeting the proposed definition of CHIP can be detected using highly sensitive error-corrected sequencing methods in almost every individual by age 50, but the clinical consequences of smaller clones are less clear.[16,17] Age-related clonal hematopoiesis (ARCH) is a term used by some clinicians and investigators to emphasize that emergence of somatically

mutated hematopoietic clones is an almost universal part of the aging process, and that most clones do not progress to hematologic malignancy. CHIP, in contrast to ARCH, requires a specific mutant allele burden, as well as that a detected somatic mutation is in a gene associated with hematologic neoplasia; ARCH can be said to include CHIP, as well as other forms of clonal hematopoiesis that are probably of less clinical significance.

Increasingly, for a variety of reasons, CHIP is detected before a hematological malignancy or cardiovascular event has occurred. How to counsel people with clonal hematopoiesis or monitor them prospectively is currently an area of uncertainty. The authors of this review each lead new specialized clinics for counseling patients with CHIP and other precursor conditions that have a risk of evolution to hematological neoplasia (Figure), and we summarize here some key biological and clinical observations with respect to clonal hematopoiesis based on published literature and our personal experience.

The following 5 scenarios indicate some of the ways in which patients with clonal hematopoiesis might end up referred to a hematologist or to a specialty clinic.

Case 1

A 49-year-old pre-menopausal woman was diagnosed with a node-negative, hormone-receptor-negative 2.1 cm ductal carcinoma of the right breast. Local resection of the tumor, adjuvant chemotherapy and radiotherapy were recommended by her oncologist. Because her mother had invasive breast cancer and a maternal aunt had ductal carcinoma in situ, germline genetic testing was recommended, and was performed on blood-derived DNA using a commercially available targeted sequencing panel focused on inherited variants pre-disposing to breast cancer, including *BRCA1, BRCA2, CHEK2, ATM* and *TP53*. The genetic testing laboratory reported that germline variants were not detected in the patient, but a TP53 p.Y234C mutation was observed at a VAF of 9%. Because most heterozygous germline gene polymorphisms or mutations are present at a VAF of 40-60% in the absence of loss of

heterozygosity, the testing laboratory reported that the TP53 variant was most likely to be somatic and acquired, rather than germline.

Case 2

During evaluation of newly diagnosed Waldenström macroglobulinemia (WM), a 61-year-old man underwent bone marrow aspiration and biopsy. The patient was previously healthy except for hypertension. Testing of his marrow mononuclear cells included next-generation sequencing using a targeted panel. The institution at which he was assessed used a single 95-gene panel assay for all hematological malignancies, which simplified electronic test ordering and laboratory workflow. In addition to a *MYD88* mutation[18] characteristic of WM at 8% VAF, a *TET2* frameshifting mutation was noted at a VAF of 21%. His marrow showed no evidence of myelodysplastic syndromes (MDS) or another myeloid neoplas, and minimal (~15%) involvement by lymphoplasmacytic lymphoma.

Case 3

A 71-year-old woman was diagnosed with squamous cell lung cancer with unilateral hilar adenopathy on radiography. As part of her staging evaluation, she underwent testing with a developmental cell-free/circulating tumor DNA assay; this assay included genes not restricted to those commonly associated with lung cancer, and the patient was incidentally noted to have JAK2 V617F at a VAF of 3%. The patient's blood counts were normal, her spleen was not enlarged, and she had no thrombosis history or constitutional symptoms.

Case 4

A 73-year-old man who is an emeritus professor of oncology at a major medical school read several papers about clonal hematopoiesis and asked his primary care physician to test him for CHIP. The patient had a normal complete blood count other than a slightly abnormal red cell distribution width (15.3%; laboratory normal range 11-14.5%). The primary care physician deferred to the oncologist's perceived broader knowledge base and ordered a gene sequencing

panel for common CHIP-associated genes. A DNMT3A p.R882H mutation was detected at a VAF of 7%.

Case 5

A 68-year-old woman with higher-risk MDS underwent allogeneic hematopoietic cell transplant from her 66-year-old fully matched brother, who had a normal blood counts prior to cell harvest. Following the transplant, full male donor chimerism was achieved, but the patient had persistent cytopenias that remained unexplained despite extensive evaluation. Marrow biopsy showed mild hypercellularity for age without dysplasia, and molecular genetic testing showed an *ASXL1* nonsense mutation at a VAF of 16% that was not present in the patient's blood prior to transplant. During subsequent evaluation, the *ASXL1* mutation was found in a blood sample from the donor as well, at a lower VAF (3%).

How does clonal hematopoiesis arise?

Somatic DNA mutations accumulate in every tissue of the body during aging.[19-22] In hematopoietic stem cells, exonic mutations occur on the order of 1 mutation per decade of life, and a small subset of these will provide a fitness advantage and result in clonal expansion.[23] Because blood cells circulate in large numbers while cells derived from other tissues subject to greater anatomical constraints do not, clonal hematopoiesis has distinct clinical implications compared to non-hematologic somatic mosaicism.[1,24]

The most common biochemical mutational event giving rise to clonal hematopoiesis is spontaneous deamination of methylated cytosine at CpG dinucleotides resulting in generation of thymine, which is not appropriately repaired and is then stably passed on to daughter cells.[25] Stable DNA alterations due to nonhomologous end-joining and large chromosomal structural rearrangements also occur. Murine models have been helpful in illuminating the precise mechanisms by which some of these mutations result in clonal expansion, but incompletely model clonal hematopoiesis, especially that associated with splicing mutations.[26]

The population prevalence of clonal hematopoiesis depends on the detection technique used. Currently used whole-exome and whole-genome approaches are insensitive for detecting clones <5-7% VAF, while targeted sequencing panels can routinely detect mutations down to a VAF of 1-2%. Using high sensitivity error-corrected targeted sequencing, clones <0.1% VAF can be found, and virtually all individuals will have evidence of this degree of clonal expansion by age 50 years.[1] However, the clinical significance of very small (<1% VAF) clones is unclear. Clones that are >10% VAF and that are associated with a splicing mutation or with more than one leukemia-associated driver mutation are associated with an increased risk of clonal progression, compared to smaller clones or those defined by a single mutation.[27]

Who is at risk for clonal hematopoiesis?

Since mutation acquisition is cumulative and time-dependent, the dominant risk factor for clonal hematopoiesis is aging, as for most myeloid and many lymphoid neoplasms.[28] Modest increases in the prevalence of CHIP have been described in males, individuals of Hispanic ethnicity, and smokers.[2,3] Some somatic mutations are more likely to be observed in specific clinical settings (Table 2).

Germline loss of the *MBD4* gene encoding the enzyme methyl-CpG binding domain 4 DNA glycosylase, important for repair of this class of DNA mutation, leads both to an increased likelihood of both clonal hematopoiesis and MDS or acute myeloid leukemia (AML), as well as to a markedly increased mutation burden (primarily cytosine to thymine transitions, as expected) when AML develops.[29] There are likely to be numerous germline predispositions to clonal hematopoiesis other than *MBD4* loss, which is rare. An intronic polymorphism in the *TERT* gene encoding telomerase reverse transcriptase, for example, is associated with an increased risk of clonal hematopoiesis, including clonal hematopoiesis measured by somatic mutation burden outlier state on whole-genome sequencing rather than leukemia driver mutation state.[30] Polymorphisms in *MPL, FRA10B,* and *TM2D3-TARSL2* are associated with somatic mosaicism at the autosomal chromosomal level.[31]

Recently, 156 germline genetic determinants of acquired loss of chromosome Y in males were identified in the UK Biobank population (~205,000 persons) and then validated in 757,114 men of Japanese or European ancestry; these variants were enriched for genes encoding factors involved in cell-cycle regulation and cancer susceptibility.[32] Furthermore, in a study of 500 sibling allogeneic hematopoietic cell transplant donors aged 55 years or older, 16% of donors had CHIP, with a median VAF of 5.9%: 19.2% of donors for recipients with myeloid neoplasm, compared to only 6.3% of donors for siblings with lymphoid malignancies.[33] Given the relative myeloid bias in malignancies arising from CHIP, this suggests a common pre-disposition (genetic or environmental) to clonal hematopoiesis in sibling pairs.

Individuals with immune-mediated marrow failure frequently have clonal hematopoiesis, including mutations in *PIGA*, which is associated with paroxysmal nocturnal hemoglobinuria.[34] A special case is clonal hematopoiesis with somatic variants in *TP53* or *PPM1D*, as such pre-existing clones are strongly selected for in patients undergoing cytotoxic chemotherapy or radiotherapy.[35-37] Clonal hematopoiesis marked by these genes at the time of cytotoxic therapy is a major risk factor for subsequent development of therapy-related MDS/AML.[38,39] In the future, knowledge of the presence of *TP53* mutant clones may influence decision-making about adjuvant therapy.[40]

What are the clinical consequences of clonal hematopoiesis?

It is important to keep in mind that many people with clonal hematopoiesis will experience no consequences; thus, CHIP could be considered a biological state that can is a risk factor for disease, not a disease itself. Acquisition of a secondary driver gene mutation may result in progression to overt malignancy.[41] While the relative risk for myeloid disease in patients meeting the definition of CHIP is high (>10) in part because of the low incidence of these neoplasms in the general population, the absolute risk is estimated at between 0.5-1% per year.[2,3]

Clonal hematopoiesis is associated with poorer outcomes after autologous transplantation.[42] In the allogeneic transplant setting, use of a donor with CHIP was associated with unexplained cytopenias in one series[43] and with more frequent development of chronic graft-versus-host disease (Hazard Ratio (HR) 1.7, 95% Confidence Interval (CI), 1.2 to 2.5) and higher non-relapse mortality, but lower malignancy relapse rate (HR 0.6, 95% CI, 0.4 to 0.9), such that there was not a clear effect of donor CHIP status on survival, in another series.[33] It is possible that donors with clonal hematopoiesis are a risk factor for donor-derived leukemias, but it is difficult to eliminate a contribution from an abnormal recipient microenvironment that permits clonal outgrowth.[44,45]

Patients with aplastic anemia harboring certain types of clones (i.e., with mutations other than *PIGA, BCOR,* or *BCORL1)* have a poorer prognosis, higher rate of evolution to MDS or AML, and lower response to anti-T cell immunosuppressive therapy.[34] *JAK2* is the 4th or 5th most commonly mutated gene in clonal hematopoiesis, as in Case 3 above, and is associated with an increased risk of arterial and venous thrombosis in addition to evolution to an overt myeloproliferative neoplasm.[46] JAK2 and other blood compartment-restricted mutations (eg KRAS) are recurrently detected in patients with non-hematological neoplasms with commercially available cell-free/circulating tumor DNA assays.[47]

Patients with unexplained cytopenias despite thorough hematology evaluation including marrow examination are frequently said to have “idiopathic cytopenias of undetermined significance” (ICUS).[48-50] While assessment of unexplained cytopenias is beyond the scope of this review, patients with unexplained cytopenias in association with clonal hematopoiesis (so-called “clonal cytopenias of undetermined significance” (CCUS) have a markedly increased risk of progression to MDS or AML diagnosed using World Health Organization criteria, compared to those with ICUS without a clonal marker.[51] For example, Luca Malcovati and colleagues reported results from long-term follow-up of patients with cytopenias who had a nondiagnostic bone marrow aspirate and biopsy at initial evaluation. The investigators showed that the presence of a clonal mutation was highly predictive of the risk of transformation to hematologic

malignancy (HR 13.9; 95% CI 5.4–35.9; 5-year and 10-year cumulative probabilities of progression, 82% for CCUS vs 9% for ICUS and 95% vs 9%, respectively). [51]

Strikingly, patients with clonal hematopoiesis have an increased risk of cardiovascular events (HR 1.9, 95% CI, 1.4 to 2.7), and clonal hematopoiesis carries a similar order of magnitude of cardiac risk as traditional risk factors such as smoking, hyperlipidemia, and hypertension.[7,12,52] The mechanism by which clonal hematopoiesis contributes to myocardial infarction and stroke is thought to be pro-inflammatory pro-atherogenic interactions between circulating clonal monocytes/macrophages and the endothelium or nascent atherogenic plaques. This process can be blocked in pre-clinical models by inhibitors of the NLRP3 inflammasome.[7,10] Clonal hematopoiesis is also associated with worse clinical outcomes in the setting of congestive heart failure[13], probably due to altered ventricular remodeling by infiltrated clonal monocytes/macrophages, also in an NLRP3-dependent fashion. Other clinical associations between non-hematologic disease and clonal hematopoiesis are being sought by multiple research groups.[53] Murine models suggest that the gut microbiome may influence the risk of clonal progression.[54]

Who should be notified of clonal hematopoiesis?

In the absence of established interventions to eliminate expanded clones, the benefit of testing for and informing patients of an incidental finding of clonal hematopoiesis is still unclear, particularly when considering the potential psychologic impact of such an unmodifiable risk factor for disease. Currently, we cannot recommend universal notification of patients about all hematopoietic clones, given that many clones will be of no consequence.

However, there are likely some settings where notification should be considered. For example, individuals may be found to have CHIP with clinical or mutational features associated with higher risk of hematologic malignancy, such as abnormal blood count indices or high-risk mutational characteristics (chromosomal aneuploidy, higher VAF of somatic mutations, or more than one known myeloid neoplasm driver mutation - especially in higher risk genes such as

IDH1/2, *TP53*, or spliceosome components). In these settings, we recommend that patients and their care team consider notification, especially if evaluation for an occult hematologic disorder might be warranted. Additionally, given the high risk of cardiovascular disease confirmed by the JAK2 V617F mutation, disclosure of CHIP related to this mutation should be strongly considered. The decision to notify individuals about CHIP should take into account the patient's life expectancy, personal preferences, and local cultural context. We recommend that the potential to discover clonal hematopoiesis be included in consent discussions for genetic testing whenever possible, and that individuals be given the option to be informed or not be informed of CHIP as an incidental finding.

How might clinical consequences of clonal hematopoiesis be averted?

Elimination of expanded clones by a targeted therapy or selective immunotherapy in order to prevent subsequent evolution to a neoplasm is not yet feasible but is an attractive goal. However, given the relatively low rate of neoplastic progression or other clinical consequences of clonal hematopoiesis, adverse effects of treatment aimed at clone elimination must be carefully considered and may prove to be justified in only certain cases.

Existing therapies for myeloid neoplasia such as DNA hypomethylating agents or lenalidomide are unlikely to be selective enough or have a favorable risk-benefit balance when used in the setting of most CHIP cases, but these drugs might one day be found to reduce overall clonal burden and delay disease onset in certain cases with large clones, and that could ultimately prove to be beneficial. Among targeted agents, splicing inhibitors (e.g., E7820[55], H3B-8800[56]) or isocitrate dehydrogenase (IDH) inhibitors are attractive, although splicing and IDH mutations are far less common CHIP-associated variants than *DNMT3A, TET2* or *ASXL1*. An interventional trial of intravenous vitamin C in TET2 mutant CCUS (NCT #03682029) is ongoing and was prompted by the observation that TET2 function can be restored and aberrant leukemic stem cell self-renewal disrupted with high concentrations of vitamin C in pre-clinical models; orally administered vitamin C does in contrast not typically achieve a high enough concentration to meaningfully alter TET2 function.[57]

From a public health standpoint, the cardiovascular risk associated with clonal hematopoiesis is of greater consequence than relatively rare neoplastic progression.[52] Anti-inflammatory approaches may be helpful in preventing cardiac events; atherosclerosis has long been recognized as an inflammatory disease[58,59], and clonal hematopoiesis may provide one mechanism linking inflammation and atherosclerosis. In a randomized placebo-controlled trial (CANTOS) of the anti-interleukin 1β antibody canakinumab in 10,061 patients who previously had a myocardial infarction and had an elevated C-reactive protein, canakinumab prevented recurrent cardiovascular events and stroke.[60] A post-hoc sequencing analysis of pre-treatment samples from nearly 4,000 patients enrolled in CANTOS found that this benefit was largely confined to subjects with CHIP, especially TET2 mutant CHIP, which was (perhaps not coincidentally, as DNMT3A might drive inflammation to a lesser degree[61]) the most common clonal mutation in this post-myocardial infarction population.[62] More recently, a placebo-controlled study of the anti-macrophage agent colchicine in 4,745 patients with a myocardial infarction history also showed benefit in preventing recurrent cardiac events; these patients have not yet been analyzed for clonal hematopoiesis.[63]

For now, monitoring of blood counts and control of recognized risk factors for cardiac disease are the main approach to patients with clonal hematopoiesis. Key questions remain unresolved. For example, which patients should undergo marrow aspiration at the time of initial assessment, and what is the optimal frequency of prospective blood count monitoring depending on the patient's specific progression risk?[40] It seems likely that a patient with CCUS and multiple high-VAF mutations including a splicing variant should be monitored more frequency than, for instance, someone with only a 2.5% VAF DNMT3A non-R882 mutant clone, but there is no consensus on specific approaches.

In addition, the optimal lipid and blood pressure goals for patients with clonal hematopoiesis and which patients should undergo additional with exercise stress testing or computed tomography coronary calcification assessment remain uncertainties. Increasingly, patients with

clonal hematopoiesis will be candidates for interventional clinical trials to mitigate both hematological and cardiovascular risk.

Finally, as with other conditions in which a "watchful waiting" or active surveillance approach is undertaken[64], a subset of patients will understandably become anxious or worried when learning about clonal hematopoiesis. Patients may also worry about losing eligibility for life or health insurance, or about the logistics of monitoring. Having a plan for psychosocial and other assistance of those with higher levels of anxiety is essential.

How to create a "CHIP clinic"

A number of institutions are now considering creating specialty clinics for assessment of patients with clonal hematopoiesis, and the clinicians and administrators undertaking this effort are encountering recurrent challenges. We can learn from each other's experiences.

Because there may be uncertainty in some cases about whether a detected variant is germline or somatic[65,66], especially with high VAF TP53 mutations (>40%), access to geneticists who can arrange for testing of non-hematopoietic tissue (e.g., by skin biopsy and creation of a fibroblast cell line as a germline control) and address non-hematological consequences of germline variants and familial considerations is important. Likewise, collaboration with cardiovascular specialists is essential, given the high risk of cardiovascular events in patients with CHIP. Growth in the field of cardio-oncology may facilitate referral. If other disease states such as autoimmune conditions or neurodegenerative disorders turn out to be increased in persons with CHIP, then close collaboration with specialists in other groups may become necessary, too.

In some institutions and clinical settings, especially where genetic testing is performed uncommonly for the reasons described above, there may not be enough patients yet to justify creation of a specific clinic or service dedicated to CHIP and related states. In these settings, partnerships with hematologists interested in other malignancy "precursor" states (e.g., monoclonal B cell lymphocytosis, monoclonal gammopathy of undetermined significance

(MGUS)) may help secure adequate institutional resources and assure a more stable and predictable referral population.

At Dana-Farber Cancer Institute (DFCI), for example, we have partnered with colleagues who are formally studying monoclonal gammopathies and the transition from MGUS to smoldering myeloma to multiple myeloma[67] – a process that has some parallels with CHIP as a precursor state to malignancy that can cause non-oncologic problems (e.g., amyloidosis, metabolic bone disease or renal injury in the case of MGUS/smoldering myeloma) – to create a "Center for Prevention of Progression (CPOP) of Hematological Malignancies", locally called the "Precursor Clinic".[68] We have benefitted from collaboration of an enthusiastic group of cardiologists at Brigham & Women's Hospital who have a long-standing interest in atherosclerosis as an inflammatory disease[58], as well as a large and experienced cancer genetics clinical group.

At Memorial Sloan Kettering Cancer Center (MSKCC), we routinely perform parallel sequencing, in which a primary tumor (e.g., solid tumor) is sequenced while blood is sequenced as a "control" to rule out germline variants including rare SNPs. (This approach is not standard at DFCI.) Because up to 30% of individuals tested will have clonal hematopoiesis, a substantial number of patients are referred by solid tumor specialists for hematology assessment.[36,69] In addition, patients with non-hematological neoplasms are commonly seen by our hematology or leukemia services for evaluation of prolonged or pronounced cytopenias in the setting of oncologic therapy. Assessment for acquired mutations associated with myeloid neoplasia is frequently performed in this setting and commonly reveals clonal hematopoiesis. As at DFCI, at MSKCC we focus on management of cardiovascular risk factors as well as blood count monitoring, and have developed an algorithm for management of CHIP in patients with solid tumors.[40] We are developing genotype-specific trials for subtypes of clonal hematopoiesis.

Billing and coding considerations

From a practical standpoint, there is no International Statistical Classification of Diseases and Related Health Problems (ICD) code for clonal hematopoiesis (at least in the version currently most widely used in the US, ICD-10-CM), and this absence of a billable code may influence reimbursement for consultation of patients with CHIP. If evaluated patients have a cytopenia, they can be classified accordingly, but those in whom CHIP has been identified may not fall into a specific category. We sometimes code patients using "Z15.09: Genetic susceptibility to other neoplasm" or "Z15.89: Genetic susceptibility to other disease", and in our experience reimbursement rates have been high with this approach. However, a genetic susceptibility code is not usually enough to justify cardiology referral. The economics and logistics of DNA sequencing in clinical practice are beyond the scope of this review, but deserve careful consideration as well.

Management of Described Cases

Case 1, the 49-year-old woman with breast cancer, reported that she was told by her treating medical oncologist that since the detected TP53 variant was not germline, it was of no clinical significance. Therefore, the patient underwent planned adjuvant chemotherapy and experienced more cytopenias than expected, although hemoglobin and neutrophil counts eventually recovered to normal. She then self-referred herself for hematology consultation following completion of adjuvant radiotherapy, at which time the VAF of the TP53 variant had increased to over 30% and she had an elevated MCV and persistent mild thrombocytopenia. This patient's expected increment in survival from the adjuvant therapy for breast cancer was <5%, while the likelihood that development of t-MDS/AML was accelerated by the adjuvant therapy is greater than that.[4,36,38] In the future, we anticipate that information about clonal hematopoiesis could be part of informed discussion with patients about the risks and benefits of adjuvant therapy.

In **Case 2** with newly diagnosed WM and a TET2 clone that is almost certainly distinct from the WM clone, yet normal blood counts and cell morphology, the patient is being monitored with blood counts 1-2 times per year; blood counts remain normal after 3 years. His hypertension is now optimally controlled. The patient underwent an elective stress test without any evidence of ischemia.

Case 3, the patient with lung cancer and an incidentally discovered JAK2 mutation, underwent successful surgical excision of her primary tumor with careful attention to venous thromboembolism prophylaxis peri-operatively. Serum erythropoietin level was normal. She elected to take low-dose aspirin indefinitely but was not felt to have an indication for cytoreductive therapy. Her blood counts are being monitored periodically and she has not experienced a complication.

Case 4, the emeritus professor with a DNMT3A mutation, struggles with fears about his future. He has advised several of his colleagues not to undergo genetic testing, and says, "Sometimes it is better not to know."

Case 5, the patient with donor-derived clonal hematopoiesis after allogeneic transplant from an older sibling, is being managed expectantly. If there is clonal progression and a second transplant needs to be undertaken, an alternative donor will be sought. Transplant programs differ in their approach to screening older donors for CHIP, and this complex topic is the subject of an upcoming *Blood Advances* point-counterpoint. While CHIP is more common in older donors, recent data indicate that small clones can be detected with sensitive error-corrected sequencing techniques in a large proportion of younger donors (clones with a median VAF of 0.,00247 were found in 44% of 25 donors with a median age of 36 years), and these clones usually engraft in the recipient and expand over time – yet donor-derived leukemia is rare.[70]

Conclusion

Clonal hematopoiesis is increasingly recognized and carries a risk of both clonal progression and cardiovascular death. Factors contributing to initiation of clonal expansion and drivers of clonal evolution are incompletely understood. The optimal management of affected persons beyond blood count monitoring and control of cardiovascular risk factors remains unclear, and is an area of active investigation.

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Figure caption

People with clonal hematopoiesis may be identified in a number of different ways, including testing done for other conditions. Tasks for hematologists include helping affected persons understand clonal hematopoiesis and its implications, organizing further diagnostic testing that may be indicated (e.g., bone marrow aspiration and biopsy), and developing a monitoring plan. Referral to other specialists may be necessary, including geneticists (e.g., if a germline mutation is possible) and cardiovascular disease specialists for traditional risk factor assessment and modification.

Table 1 Hematologic malignancies observed in representative studies of clonal hematopoiesis

Reference	Sequencing approach	Hazard ratio for development of hematologic cancer with clonal hematopoiesis (95% Confidence interval)	Number of cases of hematologic malignancy	Malignancy Types	
Jaiswal S et al., *N Engl J Med* 2014[2]	Whole exome	11.1 (3.9-32.6)	16	6 Lymphoma NOS; 4 Leukemia NOS; 2 Unspecified; 2 MM; 1 MDS;1 AML	31%
Genovese G et L., *N Engl J Med* 2014[3]	Whole exome	12.9 (5.8-28.7)	37	22 Not Listed; 3 CLL; 2 MDS; 2 MPN NOS; 2 AML; 1 Lymphoma NOS; 2 MM or other plasma cell neoplasm; 1 CMML; 1 Acute leukemia NOS; 1 Chronic leukemia NOS	42%
Jacobs K et al., *Nature Genetics* 2012[5]	SNP array	35.4 (14.7-76.6)	43	Incident hematologic cancer diagnoses not specified	NA
Laurie C et al., *Nature Genetics* 2012[6]	SNP array	10.1 (5.8-17.7)	105	38 Lymphoma; 19 MM; 14 MDS; 10 CLL; 7 AML; 4 Lymphoid leukemia NOS; 3 MPN NOS 3 Myeloid leukemia NOS; 2 CMML; 1 Hairy cell leukemia; 1 MF; 1 CML; 1 ALL; 1 Leukemia NOS	14%

Abbreviations: SNP, single nucleotide polymorphism; NOS, not otherwise specified; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; CMML, chronic myelomonocytic leukemia; CML, chronic myeloid leukemia; MM, multiple myeloma; MPN, myeloproliferative neoplasm; CLL, chronic lymphoid leukemia; MF, myelofibrosis

Table 2: Clonally restricted mutations observed in specific clinical settings in the absence of overt neoplasia

Clinical setting and reference(s)	**Gene(s)**
Aging-associated: Aging-related clonal hematopoiesis (ARCH) or clonal hematopoiesis of indeterminate potential (CHIP)[2-4,16,17]	*DNMT3A, TET2, ASXL1, JAK2, TP53*; many others are recurrent but less frequent
History of chemotherapy / radiotherapy[35,36]	*TP53, PPM1D*
Aplastic anemia[34]	*BCOR, BCORL1, PIGA; DNMT3A, ASXL1*
Severe congenital neutropenia or Shwachman-Blackfan-Diamond syndrome[71,72]	*CSF3R, TP53*
Unexplained monocytosis[73]	*ASXL1, CBL, DNMT3A, NRAS, RUNX1*

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