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REVIEW

Clonal hematopoiesis in cancer

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Clonal hematopoiesis is a common premalignant condition defined by the abnormal expansion of clonally derived hematopoietic stem cells carrying somatic mutations in leukemia-associated genes. Apart from increasing age, this phenomenon occurs with higher frequency in individuals with lymphoid or solid tumors and is associated with exposures to genotoxic stress. Clonal hematopoiesis in this context confers a greater risk for developing therapy-related myeloid neoplasms and appears to contribute to adverse cancer-related survival through a variety of potential mechanisms. These include alterations of the bone marrow microenvironment, inflammatory changes in clonal effector cells and modulation of immune responses. Understanding how clonal hematopoiesis drives therapy-related myeloid neoplasm initiation and interactions with non-myeloid malignancies will inform screening and surveillance approaches and suggest targeted therapies in this vulnerable population. Here, we examine the clinical implications of clonal hematopoiesis in the cancer setting and discuss potential strategies to mitigate the adverse consequences of clonal expansion.

The acquisition of somatic mutations in hematopoietic stem cells (HSCs) that then propagate to the point of detection describes a premalignant state aptly termed *clonal hematopoiesis*. Although we have known about this concept for more than two decades, we did not have the tools with which to understand its remarkable prevalence and, consequently, its clinical significance. Over the past decade, rapid advances in the genetic understanding of clonal hematopoiesis, first with neoplastic conditions, then in otherwise normal individuals, have underscored how often it arises and how it can affect health and well-being. Clonal hematopoiesis in isolation is associated with a small increase in the risk of developing a hematologic neoplasm and a greater risk of cardiovascular mortality when driven by mutations in myeloid malignancy-associated genes [1–3]. However, the clinical significance of clonal hematopoiesis is strongly dependent on the context in which it occurs [4,5]. Of particular interest is the impact of clonal hematopoiesis in the cancer setting. The absolute risk of progression to a hematologic malignancy is low when clonal hematopoiesis is found in healthy individuals. This is in contrast to the increased risk of developing hematologic malignancies and an apparently independent, cancer-related mortality risk when clonal hematopoiesis is found in the cancer population [6–9]. The influence of advanced age for developing clonal hematopoiesis may be less pronounced when considered in the context of diverse genotoxic insults that are more prevalent in cancer cohorts. Ongoing research into how clonal hematopoiesis might affect cancer development and response to therapy raises questions related to screening, surveillance and risk-directed therapeutic approaches for high-priority groups. Translating the oncologic implications of clonal hematopoiesis into patient care will mandate consensus-based clinical guidelines on multiple fronts and will be spurred on by novel research focused on chemoprevention.

Here we review the prevalence of clonal hematopoiesis in the cancer setting. We explore its impact on cancer-related survival, potential underlying mechanisms, how genotoxic stressors contribute to malignant clonal

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evolution, and how we might use clonal hematopoiesis to inform future opportunities for cancer prevention and risk reduction.

Clonal hematopoiesis in the cancer setting

Research into clonal hematopoiesis and our understanding of its scope has grown significantly over the past 5 years since interest in this phenomenon was rekindled. We know clonal hematopoiesis represents a highly prevalent, age-related premalignant condition and is an important risk factor for cardiovascular mortality in the general population. We know less about how clonal hematopoiesis evolves over time or how to mitigate its progression in those at highest risk. We believe that selective pressures can further shape clonal architecture after the establishment of clonal hematopoiesis to promote subsequent evolution to frank malignancy and perhaps even coincident tumor progression. In the cancer setting, the development and evolution of clonal hematopoiesis appear to be driven by genotoxic stress. Recent studies suggest clonal hematopoiesis is more prevalent in cancer cohorts by virtue of previous exposure to mutagenic stressors including chemotherapy and radiation [6–9]. There is also evidence that patients with congenital cancer predisposition mutations in DNA repair genes may be at increased risk of developing therapy-related myeloid disorders and, presumably, the clonal hematopoiesis that precedes it clinically [10–12].

Additional risk factors for clonal hematopoiesis, both in those with and in those without cancer, include current or former smoking and potential exposure to environmental mutagens. There also appears to be a germline predisposition that plays a role in the development of clonal hematopoiesis. A large study involving whole-genome sequencing of an Icelandic population found that individuals with evidence of clonal hematopoiesis were more likely to carry germline polymorphisms near *TERT*, the gene encoding telomerase [13]. An independent study focused on people with clonal hematopoiesis defined by somatic *JAK2* V617F mutations also identified enrichment for polymorphisms near the *TERT* gene in addition to well-known single-nucleotide polymorphisms near *JAK2* itself and, to a lesser extent, near the *TET2* gene [14]. *TET2* is the second most frequently mutated gene in *JAK2* mutant myeloid neoplasms although it was not sequenced in this study. However, there is evidence that *TET2*-mutant clonal hematopoiesis demonstrates familial aggregation, suggesting a congenital predisposition to acquired mutations in this gene [15].

Clonal hematopoiesis in patients with cancer has some fundamental differences when compared with otherwise healthy normal individuals. Although there is still a strong age dependence, the prevalence of clonal hematopoiesis after cancer therapy appears greater even in the absence of cytotoxic chemotherapy exposure [6].

Clonal hematopoiesis in lymphoid malignancies and solid tumors

There exists variation in the rate and type of clonal hematopoiesis seen in patients with different forms of cancer. This may reflect underlying susceptibilities to various cancer types as well as distinct treatment approaches for different tumors. A hallmark study of relapsed and refractory lymphoma patients slated for autologous stem cell transplantation identified a high rate of clonal hematopoiesis exceeding 40% for patients older than 60 [7]. Compared against persons with incidentally identified clonal hematopoiesis, mutations of *TP53* and the related gene, *PPM1D*, were highly enriched in these lymphoma patients who had been heavily exposed to cytotoxic chemotherapy. Patients with *PPM1D* mutations were more likely to have received greater doses of doxorubicin, for example.

Lymphoma patients with clonal hematopoiesis had a modest increase in their absolute risk of developing a therapy-related myeloid neoplasm that was insufficient to explain the much greater differences in other clinical outcomes, including overall survival. Stem cell mobilization was inferior in patients with clonal hematopoiesis, and there was a small, nonsignificant trend toward greater rates of relapse. However, patients with clonal hematopoiesis were more than twice as likely to die without relapse, particularly if they carried a somatic mutation in *PPM1D*. This striking difference was independent of lymphoma type, prior therapy, and age. However, patients with more than one somatic mutation and greater variant allele frequency (VAF) had the greatest risk. This study highlights that cytotoxic therapy selects for clonal hematopoiesis driven by particular somatically mutated genes and how this entity is a powerful biomarker for adverse clinical outcomes.

Greater rates of clonal hematopoiesis are similarly observed in patients with solid tumors where there are also differences in clinical outcomes. In a cohort of more than 8,800 solid tumor patients who underwent pair tumor/blood sequencing, 25% carried one or more somatic mutations consistent with clonal hematopoiesis [6]. The average age of this cohort was 58 years, indicating that the rate of clonal hematopoiesis in this population was more than three times that measured in unselected persons with clonal hematopoiesis. As with the lymphoma patients, solid tumor patients with clonal hematopoiesis were older and were enriched for mutations in *TP53* and *PPM1D* in the subset with a history of prior cytotoxic therapy. Blood cell measurements were similar between groups, suggesting little impact of clonal hematopoiesis on cell counts. As expected, rates of therapy-related myeloid neoplasms were higher in those with clonal hematopoiesis, but the absolute risk was very low (~1% after 18 months of follow-up). Blood cancers could not explain the lower median overall survival seen in solid tumor patients with clonal hematopoiesis driven by mutations in typical myeloid malignancy genes.

As the cause of death in the majority of patients (~98%) was progression of their primary malignancy, it is probable that clonal hematopoiesis is associated with cancer progression and recurrence. Whether this is a causative link, as is the case for clonal hematopoiesis and cardiovascular risk, remains to be elucidated. Potential mechanisms that could underlie such an interaction include increased inflammation from clonally derived effector cells, impairment of immune function, or, more indirectly, decreased tolerance of cancer-directed therapy.

In some settings, the adverse risk associated with clonal hematopoiesis might be mitigated by changes in therapy. A recent study in multiple myeloma patients, for example, described how lenalidomide maintenance therapy abrogated the increased mortality and shorter progression-free survival often seen in those patients with clonal hematopoiesis [16–18]. Whether such approaches might be effective in other cancer contexts remains to be determined, but it does suggest that methods to manage the risks associated with clonal hematopoiesis in cancer patients could be developed.

Clonal evolution and therapy-related myeloid neoplasms

Clonal hematopoiesis itself does not appear to be sufficient to induce clonal expansion and cause hematologic disease. Tiny mutant clones can remain stable at low levels for many years without clinical consequences in healthy individuals [19]. Additional selective pressure appears to be needed for progression as we know the majority of individuals with clonal hematopoiesis do not develop a hematologic malignancy [20]. Chemotherapy is a cell-extrinsic factor that reduces the polyclonality of surviving HSCs by conferring a strong competitive advantage to cells harboring specific resistance mutations [21–23]. These surviving HSCs preferentially repopulate the hematopoietic compartment and exhibit abnormal differentiation and genomic instability potentially leading to dysfunctional hematopoiesis and ultimately leukemic transformation. Clonal hematopoiesis in this setting is defined by clones that are inherently treatment resistant and enriched for somatic mutations in *TP53* and other genes involved in the DNA damage response, subsequently increasing the risk of developing a therapy-related myeloid neoplasm [10,21,24,25]. Genetic analysis of paired antecedent and diagnostic samples from patients with therapy-related myeloid neoplasms identified patient-matched *TP53* mutations many years before disease development [24,26]. Two studies enriched for patients with previous exposure to genotoxic stressors including chemotherapy, transplant conditioning and radiation-identified recurrent mutations in *TP53* and *PPM1D,* among others [6,7]. The presence of therapy-related clonal hematopoiesis was shown to predict an increased risk of hematologic malignances and inferior survival. Similarly, two case–control studies found the presence of a detectable myeloid clone after chemotherapy exposure increased the likelihood of developing a therapy-related myeloid neoplasm [8,9]. *TP53* was among the most commonly mutated genes in these cases, and therapy-related disease was often driven by expansion of pre-existing *TP53* mutant clones. Collectively, these studies provide strong evidence that pre-existing mutant clones are selected for by chemotherapy, contrary to the historical premise that therapy-related myeloid neoplasms arise from treatment-induced DNA damage.

Clinical implications of clonal hematopoiesis in cancer patients

Adverse clinical outcomes in cancer patients with clonal hematopoiesis raise several important questions for which there are currently no clear answers. However, we do have some information to guide us and with which to propose future studies that could inform clinical decision making [22,27]. First is the question of whether we should search for clonal hematopoiesis in patients with cancer [28]. Arguments in favor of a screening approach include the greater-than-expected prevalence of clonal hematopoiesis in this population and its clear association with inferior outcomes. At the very least, this information could have prognostic significance relevant to both the physician and the patient. However, we still do not have a nuanced understanding of which mutations are most concerning and in which context they might be most adverse. Nor do we know VAF thresholds below which somatic mutations indicative of clonal hematopoiesis might be safely ignored, if any exist. Currently, we believe that having multiple myeloid malignancy driver mutations confers greater risk, as does having mutations present in high abundance as estimated by their VAF (Table 1). Most importantly, we do not have well-established interventions capable of modifying the risk associated with clonal hematopoiesis in cancer patients, making knowledge of this condition more informational than actionable.

Regardless, clonal hematopoiesis is increasingly being recognized in cancer patients even when not specifically sought out. One of the original studies to identify the high prevalence of clonal hematopoiesis examined blood and tumor samples from subjects contributing tissue to *The Cancer Genome Atlas* [29]. Variants present in the blood sample that were absent in the tumor were used to identify clonal hematopoiesis. However, it is clear that tumor-only sequencing can uncover clonal hematopoiesis as well. As tumors are sequenced with larger panels that include

Table 1. Features of clonal hematopoiesis associated with greater clinical risk

Multiple somatic mutations in myeloid malignancy genes
High variant allele frequency (>10%)
Variants in *TP53* and/or *PPM1D*
DNMT3A R882 variants
Hotspot mutation of *IDH1* or *IDH2*

myeloid malignancy genes, mutations indicative of clonal hematopoiesis are increasingly identified [30–32]. These variants often may not be described as such and simply listed along with tumor-specific mutations identified in the sample. For mutations common to both myeloid disorders and solid tumors, like those in *TP53*, there is no established way to determine the source of mutation without additional testing. On the other hand, a low-VAF *DNMT3A* truncation mutation identified in a colon cancer sample may not have any clinical consequence, making this distinction less critical in some cases. Yet, as more targeted therapies become available for myeloid malignancies, such as those targeting *IDH1, IDH2* and *TP53* mutations, there is a risk that these agents might be used off-label to treat the solid tumor when the variant is actually present in only the blood. For example, some commercial tests have listed hypomethylating agents as treatment options for patients with *TET2* mutations, even though these lesions are more likely to be indicative of clonal hematopoiesis than solid tumor lesions. This distinction is particularly problematic for cell-free DNA assays, or liquid biopsies, in patients with solid tumors, where it may be more difficult to discriminate between tumor and blood as the source of the mutation [33–36]. Therefore, one could consider routinely sequencing blood cells to establish whether or not a potentially actionable variant is truly in the tumor or indicative of clonal hematopoiesis. Cancer patients are often tested for germline mutations in genes that predispose to malignancy, some of which can drive clonal hematopoiesis when somatically mutated. As the DNA used in these tests typically comes from blood, it can lead to the incidental discovery of mutations in genes like *TP53*, which may be enriched in this population likely to have received cytotoxic therapy [34,37]. How to appropriately counsel these patients and others in whom clonal hematopoiesis is discovered is not clear, but raises several important questions.

How should physicians manage an incidental finding of clonal hematopoiesis in cancer patients?

Preliminary consensus recommendations do exist and can provide some guidance. In the perspective by Bolton et al. [27], universal reporting of incidental clonal hematopoiesis is not recommended. In the setting of normal marrow function, cancer patients with clonal hematopoiesis driven by single mutations in non-adverse genes at low abundance (VAF <10%) need not be informed of this finding. Even when there are abnormal blood counts, careful examination for alternative causes should be made to avoid inappropriately classifying a patient as having an unexplained clonal cytopenia (Figure 1). If no alternative cause is identified and the cytopenia is clinically meaningful (e.g., causing symptoms or interfering with treatment), then a bone marrow evaluation is warranted. If the marrow study is non-diagnostic and no alternative explanation is identified, the patient would be considered to have a clonal cytopenia of uncertain significance (CCUS), which likely carries greater risk of progression to a hematologic malignancy [38–41].

For cancer patients who lack symptoms and cytopenias but harbor larger clones (VAF >10%), adverse clones (e.g., *TP53* or *PPM1D* mutated), or multiple mutations, a discussion about the potential risk associated with these lesions is warranted (Figure 1). This would justify more closely monitoring blood counts, but in the absence of hematologic abnormalities would not require a bone marrow examination or serial DNA sequencing. The discussion of risk should also include cardiovascular consequences of clonal hematopoiesis to ensure that patients are addressing management of modifiable risk factors with their cardiologists and primary care physicians [27]. Which mutations are most concerning is likely to change as we learn more from larger studies with longer follow-up.

More difficult questions arise when cancer patients identified as having clonal hematopoiesis are expected to receive additional therapy that might further select for the mutant clone and facilitate further clonal evolution. This was the case for the lymphoma patients in the Gibson et al. [7] study who underwent an autologous stem cell transplant after clonal hematopoiesis was discovered. This might also explain their particularly poor outcome compared with other studies of solid tumor patients with clonal hematopoiesis who did not necessarily receive further therapy and had less adverse outcomes.

How should physicians advise cancer patients with clonal hematopoiesis planning to receive additional chemotherapy?

For patients with metastatic disease and a poor prognosis, the longer-term consequences of clonal hematopoiesis may not be a concern. Whether they are predisposed to greater side effects, such as marrow suppression from cytotoxic therapy, is not clear, but these are complications that can generally be managed. For adjuvant therapy where there is curative intent, there may be scenarios in which the risk of exacerbating clonal hematopoiesis exceeds the reduction in cancer recurrence risk. Patients with congenital DNA repair mutations are already at increased risk of developing a therapy-related myeloid neoplasm, and greater rates of pre-existing, adverse clonal hematopoiesis may play a role [12,42,43] For breast cancer patients, we typically quote a 0.5%–2.0% risk of developing a therapy-related malignancy [44–47]. If the perceived risk reduction for breast cancer recurrence with adjuvant chemotherapy and radiation is in this range, physicians might counsel against it. If such a patient had adverse clonal hematopoiesis, the risk of therapy-related myeloid neoplasm might be greater, necessitating a more conservative approach with respect to adjuvant therapy [48,49]. In the future, therapies that target the mutant hematopoietic clone might also be considered in this scenario [50].

This issue arises in a slightly different context when cancer patients undergoing allogeneic stem cell transplantation receive donor cells harboring somatic mutations indicative of clonal hematopoiesis. Mobilization in the donor and engraftment in the host both represent stressors that further select for the clonal population. There have been several examples of donor-derived malignancies that arose from the evolution of clonal hematopoiesis existing at the time of transplant, including some of lymphoid origin [51–54]. However, given the prevalence of clonal hematopoiesis in the population and the relative scarcity of donor-derived hematologic malignancies, the risk is unlikely to be great. Recent studies reinforce that while donor-derived clonal hematopoiesis is not uncommon, it is not necessarily associated with greater malignancy risk [54]. However, it may still affect other clinical endpoints. Currently, there is no recommendation that potential donors be screened for clonal hematopoiesis the way they might be for congenital mutations that predispose to hematologic malignancies [55]. Future studies that explore the risk associated with clonal hematopoiesis subjected to further selective stress are needed to better understand when and how it might affect clinical decision making.

Clonal hematopoiesis: potential for prevention

Inflammation is increasingly recognized as a key driver of clonal expansion, prompting many groups to propose whether therapy-related clonal hematopoiesis can be targeted by anti-inflammatory therapies to alter the natural history of malignant transformation. Inflammatory processes are postulated to promote clonal dominance wherein mutant HSCs exhibit competitive fitness and are more resistant to the suppressive effects of pro-inflammatory cytokines [56–58]. Additionally, somatically mutated cells have been shown to propagate an inflammatory bone marrow niche leading to mutant clone self-renewal and proliferation, thus establishing a positive feedback mechanism [57,59,60] In this context, therapy-related clonal hematopoiesis may be a modifiable risk factor such that restoration of a more normal HSC microenvironment may reduce the risk of developing therapy-related myeloid neoplasms and other adverse outcomes.

Several preclinical studies have suggested that atherogenic inflammation is driven and regulated by *TET2* deficiency via overproduction of the pro-inflammatory cytokine interleukin-1β (IL-1β) [3,58,61]. The CANTOS trial tested whether anti-inflammatory therapy with canakinumab, a humanized monoclonal antibody against IL-1β, could prevent recurrent cardiovascular events in high-risk patients with established atherosclerotic disease [62]. There was only a small decrease in event-free survival compared with placebo. However, subsequent sequencing of blood samples suggested that the bulk of this benefit occurred in patients with *TET2*-mutant clonal hematopoiesis [63]. An additional and unanticipated finding of this study was a reduction in rates of lung cancer in the canakinumab-treated group [64]. Whether this was associated with *TET2*-driven clonal hematopoiesis is not known but indicates that targeting IL-1β can affect malignant evolution. Animal models give us insight into how this might be achieved for clonal hematopoiesis as studies of *TET2*-knockout mice reveal that abrogation of inflammatory signaling with small molecule inhibitors is able to inhibit survival advantage of mutant clones [61]. Antibiotic therapy has similarly been shown to reduce the *Tet2*-mutant clonal burden in mice, providing pre-clinical data for potential studies in patients [65]. These lines of published evidence support a role for inflammation-targeted therapies in mitigating unfavorable effects including clonal expansion. At present, the authors are investigating the preferential anti-inflammatory effects of metformin on clonal behavior in serial patient samples collected from a high-priority population. Other groups are studying the role of cholesterol-lowering "statin" drugs. Future studies may focus on mediators of the NRLP3 inflammasome such as CD33 and S100A9 or targeting of NLRP3 itself where there is evidence for its involvement in the development of myeloid malignancies like myelodysplastic syndrome.

Molecularly targeted interventions may also be of interest for primary chemoprevention in individuals harboring clonal hematopoiesis in high-risk genes [66]. For instance, normal individuals with *IDH*-mutant clonal hematopoiesis are at very high risk of developing acute myeloid leukemia (AML) [67,68]. It may be worthwhile to consider *IDH*-targeted therapies that are currently approved for AML in this group to determine whether earlier intervention can alter the natural history of leukemic transformation. A similar approach could be proposed using APR-246 therapy for individuals with *TP53*-mutant clonal hematopoiesis. APR-246 is an alkylator of thiol groups that can covalently stabilize mutant forms of TP53, presumably restoring their normal function in vivo [69]. This could even be considered for patients with *TP53*-mutant clonal hematopoiesis requiring additional genotoxic therapy to abrogate the selective advantage of these clones. Though likely to be less AML penetrant than *IDH* and *TP53* mutations, loss of *TET2* function may be partially restored with high-dose vitamin C, which could attenuate the pro-inflammatory effects of *TET2*-mutant clones and potentially offset clonal evolution [70–72]. Most patients with clonal hematopoiesis carry heterozygous loss-of-function mutations in *TET2*, leaving the protein product of the wild-type allele available for augmentation by vitamin C [2,73]. Studies of this approach in *TET2*-mutant myeloid malignancies are ongoing.

Although these ideas remain speculative at the moment, the incidence of therapy-related myeloid neoplasms is expected to rise in parallel with the increase in cancer survivors, emphasizing the importance of chemoprevention research to mitigate the adverse consequences of our own therapies.

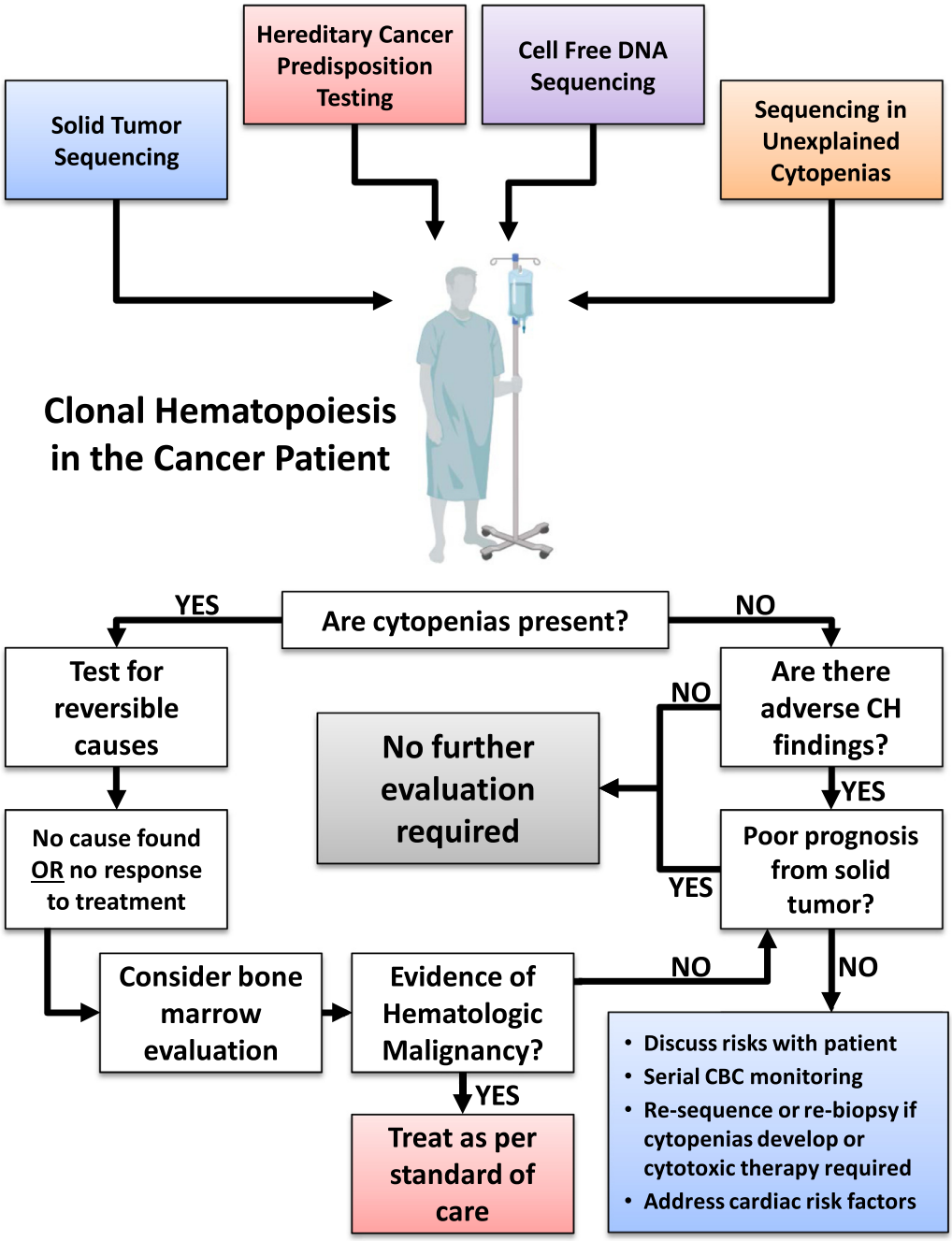

Figure 1. Authors' suggestions for evaluation and management of cancer patients identified as having CH. Adverse CH findings refer to mutational features associated with greater clinical risk as summarized in Table 1. *CBC*=complete blood count; *CH*=clonal hematopoiesis.

Conclusions

Clonal hematopoiesis has been linked to a variety of clinically significant endpoints, many of which are relevant only in specific contexts. Cancer patients have higher rates of clonal hematopoiesis perhaps because of increased predisposition to malignancy, carcinogenic environmental exposures, and treatment with clonally selective genotoxic therapies. The consequences of clonal hematopoiesis in cancer patients go beyond the increased risk of cardiovascular disease seen in the general population. They must also contend with inferior overall survival potentially driven by earlier progression of their underlying malignancy. Whether to look for clonal hematopoiesis in cancer patients is not clear, nor is it straightforward to explain its significance when it is incidentally identified. We are still learning which mutations, at what abundance, and in which clinical context merit the greatest concern. Recommendations that guide our management of these patients are in development and will likely evolve as

does our understanding of these questions. Future guidelines may also incorporate suggestions for treating clonal hematopoiesis directly so as to minimize its most adverse consequences. Research efforts aimed at informing these questions have begun and will help redefine our approach to managing clonal hematopoiesis in the cancer setting.

Conflict of interest disclosure

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