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EDITORIAL

Beyond the cancer cell: What the 2026 Hallmarks update means for precision oncology

Dirk Geerts*

Research and Development, GenDx, Yalelaan 48, 3584 CM Utrecht, The Netherlands

1. Why the Hallmarks still matter

Few conceptual frameworks have influenced modern oncology as profoundly as the Hallmarks of Cancer review series published in 2000, 2011, and 2026.[1-3] In 2000, Hanahan and Weinberg first proposed that six acquired biological capabilities could help explain the remarkable diversity of malignant tumors. These six capabilities comprised self-sufficiency in growth signals, insensitivity to anti-growth signals, apoptosis evasion, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis.[1] Rather than explaining every molecular mechanism, the framework provided a common grid for mapping the biological features of different cancers and identifying shared principles of their development and progression.

The 2011 update expanded the framework to include deregulated energy metabolism and immune evasion as emerging hallmarks, alongside genome instability and tumor-promoting inflammation as enabling characteristics.[2] Thus, the Hallmarks became an enduring way of organizing the rapidly expanding field of cancer biology.

Hanahan's 2026 synthesis, "Hallmarks of cancer—Then and now, and beyond," arrives twenty-six years after the original paper.[3] Its significance lies less in adding another hallmark to the list than in reorganizing the framework into a comprehensive description of cancer biology. For clinicians and researchers, the central question is whether this broader perspective translates into a better understanding of disease progression, treatment response, and resistance.

2. From individual capabilities to four dimensions

The framework has evolved progressively. Figure 1 illustrates this development toward an adaptive cancer ecosystem. The original paper already recognized that tumors recruit and exploit neighboring normal cells, and the 2011 update made the tumor microenvironment (TME) increasingly prominent.[1,2] In 2022, phenotypic plasticity was proposed as a ninth hallmark, emphasizing the capacity of malignant cells to change differentiation states and behavior without necessarily acquiring new driver mutations.[4] The 2026 framework contains four interconnected dimensions: (1) nine acquired functional capabilities, (2) five hallmark-enabling phenotypic characteristics, (3) the various cell populations within the TME, and (4) interactions between cancer and the whole organism.[3] Alongside genome instability and tumor-promoting inflammation, the enabling characteristics include non-mutational epigenetic reprogramming, innervation, and the microbiome.

3. Cancer as an adaptive ecosystem

A tumor is not a static collection of cells carrying a particular set of mutations. Rather, it is a continually adapting tissue whose behavior reflects interactions among genetically

***Corresponding author:**
Dirk Geerts
(d.geerts@gendx.com)

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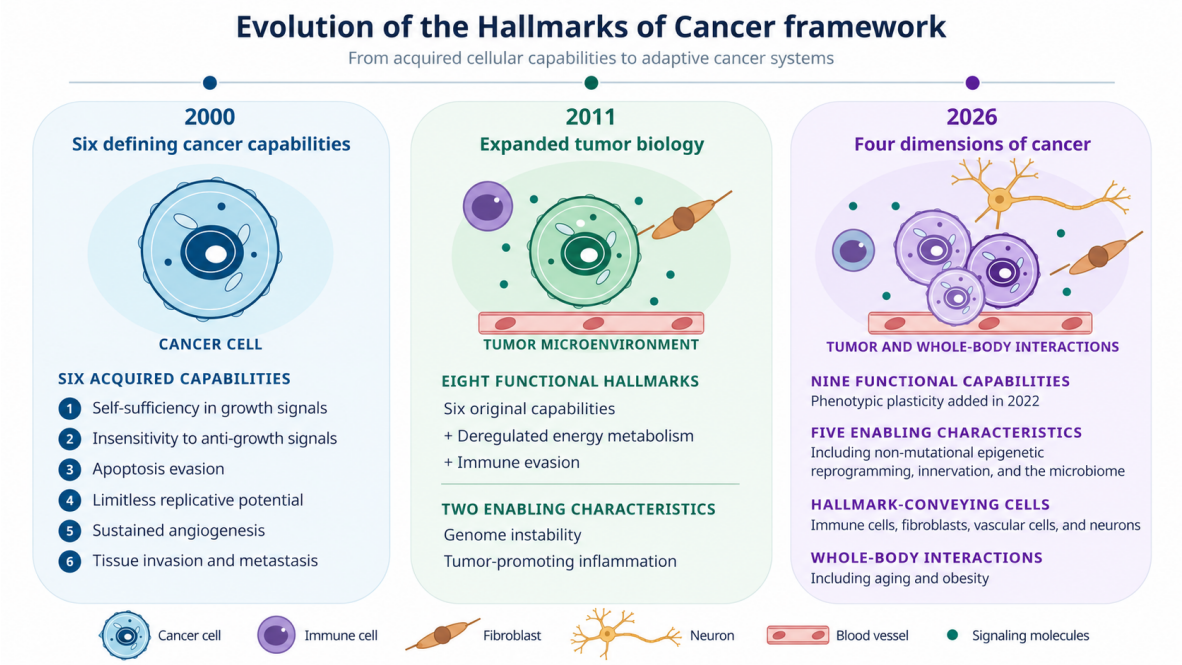


Figure 1. Evolution of the Hallmarks of Cancer framework. The 2000 model organized cancer biology around six acquired capabilities called hallmarks. The 2011 update added two additional hallmarks and two enabling characteristics, with greater emphasis on the tumor microenvironment. The 2026 synthesis integrates four dimensions: nine acquired capabilities, five enabling characteristics, hallmark-conveying cell populations, and whole-body interactions. Phenotypic plasticity, proposed as a ninth hallmark in 2022, is incorporated into this broader framework. Schematic interpretation based on the Hallmarks publications.[1-4]

and epigenetically diverse cancer cells, fibroblasts, vascular cells, immune populations, neurons, the extracellular matrix, and signals originating elsewhere in the body. The same oncogenic alteration may therefore have different consequences depending on the tissue of origin, the TME, and the stage of disease.

Phenotypic plasticity illustrates this adaptability. Cancer cells can adopt alternative states that enable them to survive nutrient limitation, evade immune attack, or withstand therapy. Immune-cell activity, in turn, is shaped by conditions within the TME, including vascular access, stromal organization, metabolic competition, and immunosuppressive signaling. These processes are interconnected and can reinforce one another or shift in response to treatment. The 2026 framework also highlights how whole-body factors, including aging and obesity, influence tumor development and progression.[3] This broader view recognizes that treatment resistance can arise both through selection of genetically resistant clones and through changes in cell states and interactions within and beyond the tumor.

I suggest that the most useful clinical application of this framework is to identify which capabilities a tumor depends on, how they interact, and which alternative routes treatment might favor. The priority is to find dependencies whose disruption could limit tumor adaptation.

4. From conceptual understanding to clinical application

This broader view also challenges precision oncology: genomic profiling is essential, but genotype alone cannot fully explain tumor behavior or predict how a cancer will adapt to treatment. Immune escape, altered differentiation, metabolic reprogramming, and interactions with neighboring cells may differ between tumors carrying similar driver mutations and may change during disease progression.

How can this broader understanding guide diagnostics, predictive biomarkers, and rational combination therapies? Tissue profiling, functional biomarkers, advanced imaging, and serial liquid biopsies offer complementary approaches. But measuring every hallmark dimension is neither currently possible nor necessarily useful. The priority is to identify features that are measurable, informative, and actionable in a given clinical context, and to distinguish promising biological hypotheses from validated predictive biomarkers.

The strength of the original Hallmarks framework was its ability to organize complexity. Its clinical application should preserve that clarity: additional biological information is only valuable when it resolves a clinical uncertainty or improves treatment decisions. The expanded framework should guide the selection of informative measurements, rather than make comprehensiveness an end in itself.

This logic also applies to treatment. Hanahan proposes targeting vulnerabilities linked to different hallmarks to limit adaptive resistance,[3] as illustrated by combining anti-angiogenic agents with immune checkpoint inhibitors in selected malignancies. Just as context shapes the effects of an oncogenic alteration, it also shapes the benefits of a therapeutic combination. Clinical use of such combinations therefore requires evidence of efficacy, acceptable toxicity, and appropriate patient selection.

5. Embracing complexity but preserving clarity

The original Hallmarks concept derived its strength from its simplicity. As the framework expands, the challenge is to preserve that clarity while ensuring that a more comprehensive account of cancer biology also improves the framework's predictive value. Its value lies not only in organizing existing knowledge, but also in generating testable hypotheses about which tumor capabilities matter most, when they matter, and how they can be disrupted.

A further challenge is falsifiability: explaining both treatment success and failure retrospectively does not establish predictive value. Before treatment, a robust test should specify which tumor dependency is expected to determine response, how the tumor might adapt, and which findings would challenge these predictions. Prospective studies could then assess whether this approach adds predictive value beyond existing clinical and molecular predictors. This would distinguish the framework's educational breadth from its utility as a guide to intervention.

The priority is not necessarily another expansion of the hallmarks catalog, but establishing whether assessing these dimensions together improves clinical decisions and whether hallmark-guided treatments outperform conventional approaches. This requires biological validation, reproducible measurements, and attention to how tumors vary across tissues, between patients, and over time.

The third-generation Hallmarks model therefore offers more than a synthesis of cancer biology: it sets a new translational agenda for diagnosis, therapy selection, and resistance management. Its lasting value will depend on whether this richer understanding helps oncology move from describing what cancer can do to anticipating what a particular cancer will do next. The framework's enduring ability to turn complexity into understanding gives us good reason to believe it can meet that challenge.

Conflict of interest

Dirk Geerts serves as an Editorial Board Member of this journal. The author declares no competing interests.

AI tools statement

ChatGPT (OpenAI) image-generation tools were used to generate Figure 1 from a template prepared by the author. All information in Figure 1 was reviewed and revised by the author, who takes full responsibility for its design and content.

References

1. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000,100(1):57-70.

   doi: 10.1016/S0092-8674(00)81683-9

2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011,144(5):646-674.

   doi: 10.1016/j.cell.2011.02.013

3. Hanahan D. Hallmarks of cancer—Then and now, and beyond. *Cell*. 2026,189(8):2254-2277.

   doi: 10.1016/j.cell.2025.12.049

4. Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discov*. 2022,12(1):31-46.

   doi: 10.1158/2159-8290.CD-21-1059