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Research Article

Early Cancer Detection Beyond Static Screening: Longitudinal Monitoring, Molecular Biomarkers, and the Limits of Precision Surveillance

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Abstract

Early cancer detection has traditionally relied on episodic screening strategies applied to broad population categories and interpreted against fixed diagnostic thresholds. Although these approaches have reduced mortality in selected settings, they generally detect disease only after anatomical, biochemical, or molecular abnormalities have become sufficiently pronounced to cross predefined cut-offs. Recent advances in genomics, liquid biopsy, and metabolomic profiling have prompted renewed interest in whether earlier detection could be improved not only by adding new biomarkers, but also by changing the logic through which biomarker information is interpreted.

This review examines several complementary dimensions of early tumorigenesis that may inform such a shift, including inherited susceptibility, somatic field evolution, circulating tumor DNA (ctDNA) dynamics, and metabolic remodeling. Germline variants may help refine baseline risk and surveillance intensity, whereas field cancerization and mutational signatures highlight that malignant transformation often develops within spatially and temporally altered tissues before overt cancer becomes clinically detectable. ctDNA offers an important tool for tracking molecular residual disease and clonal persistence, but its utility in very early detection remains constrained by low tumor shedding and biological heterogeneity. Emerging metabolomic and microbiome-related studies further suggest that volatile organic compound (VOC) profiles may reflect tumor-associated ecosystem changes, although this area remains exploratory and far from clinical standardization.

Rather than arguing for a single transformative assay, this review considers whether future early-detection strategies may benefit from combining longitudinal biomarker trajectories, individualized baseline interpretation, germline risk information, and selected multi-omic signals within risk-adapted surveillance models. At present, however, important limitations remain, including assay sensitivity in low-burden disease, false-positive management, overdiagnosis, and uneven clinical validation across platforms. Early detection is therefore better understood not as a solved technological problem, but as an evolving effort to interpret biological change earlier, more accurately, and with greater clinical discipline.

Keywords

Early cancer detection, Longitudinal surveillance, Germline susceptibility, Field cancerization, Mutational signatures, Circulating tumor DNA, Molecular residual disease, Volatile organic compounds, Colorectal cancer, Multi-omics integration, Wearable biosensors.

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Introduction

From Population Screening to Longitudinal Risk Interpretation

Cancer screening has long been organized around population-level risk categories, most commonly age and sex. Mammography, fecal immunochemical testing (FIT), prostate-specific antigen (PSA) measurement, cervical cytology, and low-dose computed tomography (LDCT) for lung cancer all exemplify this approach. These strategies have clearly improved outcomes in selected malignancies, but they remain largely episodic and threshold-based: disease is usually recognized only after anatomical, cellular, or biochemical abnormalities become sufficiently pronounced to satisfy predefined criteria. In practice, this means that screening often identifies cancer only once deviation is already measurable in relatively coarse terms.

Recent interest in multi-cancer early detection (MCED) assays has highlighted both the appeal and the limitations of trying to improve this framework through increasingly sophisticated molecular tests. Large implementation studies such as PATHFINDER showed that blood-based screening in asymptomatic individuals is feasible and can identify cancers not targeted by conventional screening programs, but they also illustrated a major practical problem: positive molecular signals may be difficult to localize or resolve clinically when imaging and standard work-up do not provide an immediate anatomical correlate [1]. Similarly, circulating cell-free DNA (cfDNA)-based assays have shown high specificity and promising performance in several tumor types, particularly when methylation or multi-analyte approaches are used [2-4].

Yet this promise should not be overstated. Performance varies markedly with tumor type, disease stage, tumor fraction, and assay design, and very early lesions may release little or no detectable material into the circulation [5]. These limitations are not merely technical. They reflect an underlying biological problem: cancer develops over time, whereas many screening strategies still rely on isolated measurements. Genomic and evolutionary analyses indicate that driver mutations and clonal expansions may precede overt malignancy by years [6]. During this interval, tissues may undergo progressive molecular and ecological change involving somatic mutation, epigenetic remodeling, altered stromal signaling, immune modulation, and metabolic reprogramming. A single cross-sectional sample can capture only one moment within that process. It may therefore miss early but persistent directional change that remains modest in absolute magnitude.

This has led to growing interest in a different interpretive model: rather than asking whether a biomarker exceeds a population threshold at a given moment, one might ask whether it has deviated meaningfully from that individual's own prior baseline. The conceptual appeal of this approach is straightforward. Many biomarkers show substantial inter-individual variability but relatively greater within-person stability over time. Under those circumstances, sustained deviation from a personal baseline may be more informative than comparison with a broad population reference interval [7]. Analogous reasoning already informs parts of cardiovascular prevention, where serial changes in blood pressure, lipids, or inflammatory markers often provide more useful risk information than isolated values interpreted without temporal context [8].

Traditional tumor markers illustrate both the potential and the caution required in this regard. Markers such as CEA, CA-125, CA19-9, PSA, and AFP have well-known limitations when used as stand-alone screening tools, largely because of insufficient sensitivity, limited specificity, and vulnerability to confounding biological variation. However, in some settings, their value improves when interpreted longitudinally rather than as single cut-off-based measurements. In ovarian cancer, serial CA-125 interpretation through longitudinal risk algorithms has performed better than fixed-threshold approaches [9]. In prostate cancer, PSA kinetics have often provided clinically relevant information beyond absolute concentration alone, although even here interpretation remains context-dependent and sometimes controversial [10]. These examples do not establish a universal solution, but they do suggest that trajectory may carry information that static thresholds obscure.

At the same time, changes in biomarkers over time should be interpreted cautiously. Longitudinal surveillance has its own limitations, including analytical variability, biological noise, incidental fluctuations, false-positive results, and the possibility of identifying indolent abnormalities that may not require intervention. Any move toward individualized monitoring would therefore require rigorous standardization, careful modeling of normal within-person variance, and clinically disciplined rules for escalation. Put differently, the challenge is not simply to measure more often, but to decide which forms of change are meaningful and which are not [7,8] (Figure 1).

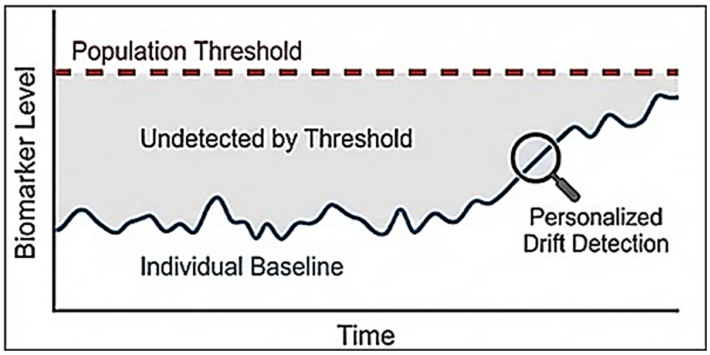

Figure 1: Static threshold-based screening versus longitudinal within-person monitoring. Traditional screening relies on population-derived thresholds. A longitudinal approach instead evaluates whether repeated measurements diverge from an individual's prior biological range.

A further reason this question has become more important is that cancer perturbs multiple biological systems simultaneously. Tumor development may affect cell-free nucleic acids, protein expression, inflammatory signaling, immune tone, angiogenesis, and systemic metabolism. This multidimensional biology has motivated multi-

analyte platforms that combine circulating proteins with mutation or methylation data. Studies such as CancerSEEK and later cfDNA methylation classifiers suggest that combining analytes can improve performance compared with single-marker strategies [2,11]. Even so, most available platforms remain fundamentally cross-sectional in clinical use. A more demanding but potentially more informative next step would be to evaluate whether repeated within-person measurement across biomarker classes could identify coordinated biological deviation before conventional diagnostic thresholds are crossed [12].

This review examines such possibility through several distinct but partially converging domains of early tumor biology: inherited susceptibility, somatic field evolution, circulating tumor DNA dynamics, and metabolic remodeling, including exploratory work on volatile organic compounds (VOCs). The aim is not to propose a unified screening solution or to imply that these modalities are ready for seamless clinical integration. Rather, the purpose is to assess what each contributes, where the evidence is strongest, and where enthusiasm currently exceeds validation. In that sense, the central question is not whether cancer screening can become more "precise" in the abstract, but which forms of longitudinal and molecular information are sufficiently robust to improve early detection without simply increasing complexity, cost, and diagnostic ambiguity [2,12,13].

Table 1: Conceptual differences between conventional screening and longitudinal biomarker monitoring. The table summarizes the core transition from traditional methods to a personalized baseline approach.

Feature	Traditional Screening	Personalized Baseline Medicine
Conceptual Foundation	Population-level risk (age, sex, limited history)	Individual biological "set point"
Diagnostic Logic	Threshold-based (static cut-offs)	Trajectory-based (dynamic drift from baseline)
Testing Frequency	Episodic (e.g., every 2–5 years)	Longitudinal / Integrated surveillance
Intervention Goal	Early clinical/anatomic detection	Molecular interception at inception

Germline Susceptibility

Predicting First and Subsequent Events

If longitudinal biomarker modeling frames early detection as the recognition of change over time, germline susceptibility frames it as a matter of baseline risk. The integration of inherited genetic information into oncology has shifted the view of cancer from a purely somatic event to a disease that may also reflect an underlying constitutional predisposition across the life course. In this setting, a first tumor may be not only an isolated clinical event, but also the first visible sign of a broader inherited vulnerability. Large sequencing studies have shown that pathogenic germline variants are present in about 8–12% of patients with solid tumors, including many patients without a striking family history [14].

This observation has supported the development of tumor-to-germline strategies, in which findings from somatic tumor profiling lead to confirmatory germline testing and, when appropriate, to long-term risk management and surveillance [14,15]. In this way, tumor profiling may uncover inherited predisposition, while germline results can influence screening intensity, screening method, and follow-up intervals for patients and, in some cases, their relatives [15,16].

Hereditary Breast and Ovarian Cancer (HBOC) syndrome provides a clear example of the life-course importance of this approach. Pathogenic variants in BRCA1 and BRCA2 are associated with cumulative lifetime breast cancer risks approaching 72% and 69%, respectively, by age 80, together with substantial risks of ovarian and contralateral breast cancer [17]. Risk remains elevated even after treatment of a first tumor, indicating that the underlying susceptibility persists. The implications extend beyond breast and ovarian cancer, because BRCA1/2 carriers also have increased risks of pancreatic and prostate cancer [16,18]. These findings have supported prevention strategies that may include earlier MRI-based breast screening, risk-reducing salpingo-oophorectomy, and, in selected settings, pancreatic surveillance [16].

The treatment landscape has strengthened this link between therapy and prevention. PARP inhibitors exploit synthetic lethality in homologous recombination-deficient tumors and have become an important targeted treatment in BRCA-associated cancers [19]. At the same time, the detection of a BRCA alteration during tumor profiling often leads to germline confirmation testing. A therapeutic finding can therefore also become the starting point for long-term risk assessment and surveillance planning.

A similar model applies to Lynch syndrome, which is caused by pathogenic germline variants in mismatch repair genes such as MLH1, MSH2, MSH6, and PMS2 [15]. Universal screening of colorectal cancers for mismatch repair deficiency, usually by immunohistochemistry or microsatellite instability testing, has made it easier to identify patients who need germline confirmation. Individuals with Lynch syndrome have substantially increased lifetime risks of colorectal, endometrial, gastric, small bowel, pancreatic, and urothelial cancers [15,20]. Even after segmental colectomy, the risk of metachronous colorectal cancer remains significant, supporting intensive colonoscopic follow-up [21]. In this setting, tumor profiling not only guides treatment choices such as immunotherapy; it can also reveal a constitutional repair defect that changes the patient's long-term screening strategy.

Beyond these high-penetrance syndromes, current genomic practice also identifies clinically important variants in other susceptibility genes. Pathogenic CDH1 variants define hereditary diffuse gastric cancer (HDGC), which is associated with high risks of diffuse gastric cancer and lobular breast cancer [22]. Because early diffuse gastric lesions are difficult to detect reliably by endoscopy, prophylactic total gastrectomy remains the most dependable preventive option in high-risk carriers [22]. In this case,

germline information may lead directly to preventive intervention rather than to surveillance alone.

Similarly, pathogenic variants in STK11 cause Peutz–Jeghers syndrome, which is associated with gastrointestinal hamartomatous polyps and increased risks of pancreatic, gastrointestinal, breast, and gynecologic cancers. These patients usually require multimodal surveillance, including pancreatic imaging from early adulthood [23].

This again shows how germline findings can change both the timing and the intensity of early detection.

The increasing use of multigene panel testing has also expanded attention to moderate-risk genes such as PALB2, CHEK2, and ATM. In some settings, interpretation of these variants may be refined by polygenic risk scores (PRS), which combine the effects of many common alleles to improve risk estimation. Large association studies have shown that breast cancer risk can be stratified across a broad spectrum, ranging from moderate-risk susceptibility genes to more complex polygenic models [24,25]. As summarized in (Table 2) this wider genetic framework supports a graded, probability-based view of early detection rather than a simple hereditary-versus-sporadic distinction.

Within the overall framework of this manuscript, germline genetics can be viewed as a prior determinant of risk that influences surveillance thresholds and testing intervals. Individuals with high-penetrance variants may require earlier and more frequent imaging or molecular testing, whereas those with lower inherited risk may be monitored with less intensive strategies. When a first tumor occurs, it becomes an important clinical event that can further refine the individual risk profile and inform subsequent surveillance. In this way, germline susceptibility extends early detection beyond the search for an emerging tumor. It places cancer risk within a life-course framework in which inherited predisposition shapes both the risk of a first event and the chance of later cancers. When combined with longitudinal biomarker assessment and somatic evolutionary analysis, germline information helps move early detection away from age-based triggers alone and toward a more biologically informed strategy.

Somatic Evolution and Field Cancerization

If germline susceptibility defines inherited risk, somatic evolution describes the tissue changes through which cancer develops over time. Cancer usually does not arise from a single isolated cellular event. Rather, it emerges through a prolonged process in which tissues gradually accumulate genetic and epigenetic alterations. The idea of field cancerization, first proposed by Slaughter in 1953 in oral squamous epithelium, suggested that large areas of tissue that appear histologically normal may already contain pre-neoplastic changes [26]. What began as a morphological concept now has strong molecular support.

With the development of next-generation sequencing, it has become clear that clonal cell populations carrying driver mutations can be detected in tissues that still appear normal under the microscope, sometimes years before cancer becomes clinically evident [27]. Analyses based on genotype-tissue-expression (GTEx)-related data have further shown that somatic mutations and clonal expansions are present across many normal tissues and tend to increase with age and exposure history [28,29]. These findings change the way carcinogenesis is understood: the visible tumor may represent only the most advanced clone within a much broader altered tissue field [6]. This has important implications for early detection. Detection cannot be limited to finding a single anatomical lesion. It also needs to take into account the evolutionary behavior of tissue compartments that may gradually move toward malignant

Table 2: Main germline susceptibility genes and syndromes relevant to risk-adapted early detection.

Syndrome / Risk Group	Primary Gene(s)	Main Associated Cancer Risks	Main Clinical Implication
Hereditary Breast and Ovarian Cancer (HBOC)	BRCA1, BRCA2	Breast, ovarian, pancreatic, prostate	Earlier and intensified surveillance; risk-reducing surgery in selected settings; PARP inhibitor eligibility in appropriate tumors
Lynch syndrome	MLH1, MSH2, MSH6, PMS2	Colorectal, endometrial, gastric, small bowel, pancreatic, urothelial	Universal MMR/MSI tumor screening; germline confirmation; intensified colonoscopic and syndrome-specific surveillance
Hereditary Diffuse Gastric Cancer (HDGC)	CDH1	Diffuse gastric, lobular breast	Consideration of prophylactic total gastrectomy in high-risk carriers; breast surveillance
Peutz–Jeghers syndrome	STK11	Pancreatic, gastrointestinal, breast, gynecologic	Multimodal surveillance, including pancreatic imaging from early adulthood
Moderate-risk hereditary breast cancer predisposition	PALB2	Breast (and, in some settings, other cancers)	Risk stratification with tailored breast surveillance; interpretation may be refined by family history and broader genetic context
Moderate-risk hereditary breast cancer predisposition	CHEK2	Breast (and selected other cancers depending on context)	Risk-adapted surveillance based on variant type, family history, and overall clinical context
Moderate-risk hereditary breast cancer predisposition	ATM	Breast (and selected other cancers depending on context)	Risk-adapted surveillance based on variant interpretation and individual/family history
Polygenic susceptibility	Polygenic risk scores (PRS)	Variable, depending on the cancer type and score used	Refinement of population risk stratification; may help identify subgroups who could benefit from more personalized screening intensity

transformation. In other words, the relevant biological unit is often not only the tumor itself, but also the surrounding field in which it develops.

Mutational signature analysis provides one way to understand these processes. Large whole-genome studies from the PCAWG consortium identified more than forty reproducible mutational signatures linked to distinct endogenous and exogenous processes. Some are associated with recognized carcinogenic exposures, such as ultraviolet radiation or tobacco smoke, whereas others reflect defective DNA repair pathways, including homologous recombination deficiency or mismatch repair loss. Others, such as SBS1 and SBS5, are associated with age and accumulate gradually over time [30].

These signatures are not limited to established cancers. Deep sequencing studies have shown that driver mutations such as TP53, NOTCH1, and KRAS can also be found in histologically normal skin, esophagus, and other tissues, with mutation burden increasing with age [31-33]. In sun-exposed skin, clones carrying cancer-related mutations can occupy substantial portions of normal epithelium [31]. These findings provide direct molecular support for field cancerization: tissues exposed to chronic mutagenic stress can accumulate cancer-associated genomic changes long before a clinically detectable tumor appears.

Mutational signatures are also clinically relevant because they connect biological mechanism with treatment response. Homologous recombination deficiency signatures, often linked to BRCA1/2-related repair defects, can identify tumors that may respond to PARP inhibition [34]. Likewise, mismatch repair deficiency signatures are associated with responsiveness to immune checkpoint blockade [35]. Thus, the same mutational processes that shape tissue evolution before tumor emergence can later inform treatment decisions once cancer has become clinically manifest.

Among driver genes, TP53 is especially important in field evolution. p53 plays a central role in the response to DNA damage by regulating cell-cycle arrest, DNA repair, and apoptosis [36,37]. Loss of p53 function allows damaged cells to survive and expand, making TP53 mutation one of the most common early events in epithelial carcinogenesis [36,37]. One of the earliest molecular demonstrations of this principle came from head and neck cancer, where identical TP53 mutations in histologically negative surgical margins were associated with later local recurrence [38]. Similar observations in Barrett's esophagus suggest that TP53-mutant clones may be present years before dysplasia or adenocarcinoma develops [39].

These observations support the idea of a persistent altered tissue field created by repeated cycles of injury, mutation, and clonal selection. Chronic exposure to ultraviolet radiation, tobacco smoke, alcohol, or inflammation does not usually generate one isolated mutation. Instead, it produces a patchwork of expanding subclones, some of which carry parts of the molecular machinery needed for malignant progression [31,33]. The final tumor can therefore be understood less as a solitary random event and more as the dominant clone emerging from an already altered biological field. This concept is illustrated in (Figure 2).

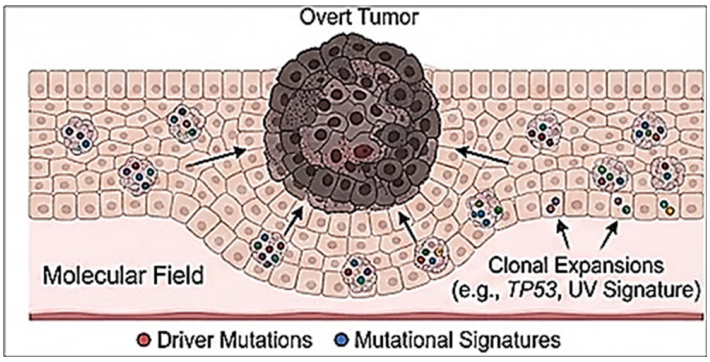

Figure 2: The molecular field of cancerization. The evolutionary landscape of field cancerization. Tissues harbor "molecular field memory"—clones with driver mutations (e.g., TP53) and mutational signatures (e.g., UV, tobacco) that precede and surround the overt malignancy.

Cancer may arise within a broader tissue field that already contains expanding clones with driver mutations and exposure-related mutational patterns. The overt tumor is then the most advanced clone within this altered field, rather than an entirely isolated lesion.

Recognition of field cancerization has direct implications for early detection. First, it helps explain why some tissues may require closer surveillance after chronic exposure or after treatment of a primary cancer. Second, it helps explain the development of metachronous tumors in the same anatomical region despite apparently complete excision of the original lesion. Third, it raises the possibility that molecular assessment of surrounding or at-risk tissue may eventually improve recurrence risk stratification beyond standard histopathology alone [38,39].

A related example is clonal hematopoiesis, in which age-related mutant hematopoietic clones expand in the absence of overt leukemia or another blood cancer. This process can precede hematologic malignancy by years and has also been associated with wider adverse outcomes [40]. Although this occurs in the blood compartment rather than in a solid tissue field, it reinforces the same general principle: somatic evolution in tissue that appears clinically normal may act as an early sign of later malignant risk.

Taken together, somatic evolution and field cancerization expand the early-detection framework beyond the simple search for a visible lesion. Germline genetics defines inherited susceptibility, while somatic mutations, clonal expansions, and mutational signatures describe how tissues change over time under cumulative stress. In this larger view, early detection includes recognition of instability within a spatially extended and evolving biological field.

Liquid Biopsy and Molecular Residual Disease

If field cancerization describes the spatial and evolutionary changes that take place in tissues before a tumor becomes visible, liquid biopsy adds a time-based dimension to this framework. The analysis of circulating tumor DNA (ctDNA) has become an important tool for post-treatment surveillance because it allows real-time monitoring of tumor-derived genetic material in blood [41]. While cfDNA includes all extracellular DNA fragments released from both normal and abnormal cell turnover, ctDNA is the tumor-derived fraction of that pool. Because ctDNA carries somatic alterations found in the primary tumor, it can serve as a molecular marker of residual clonal disease [42].

Unlike imaging, which usually detects recurrence only after a structural lesion has become large enough to visualize, ctDNA can identify residual disease months earlier. In colorectal cancer, the randomized DYNAMIC trial showed that ctDNA-guided postoperative management could reduce the use of adjuvant chemotherapy without compromising recurrence-free survival, supporting ctDNA as a clinically useful marker of molecular residual disease (MRD) [43]. Additional studies in solid tumors have shown that postoperative ctDNA positivity is strongly associated with later relapse and may precede clinical or radiologic progression [44,45]. In this setting, liquid biopsy does more than indicate whether disease is present. It also provides a way to follow the activity of residual tumor clones over time. Blood therefore becomes a practical sampling window into tumor dynamics during the period between apparent remission and overt recurrence. (Figure 3) summarizes this surveillance role. The figure is conceptual and does not imply uniform assay performance across tumor types or clinical settings.

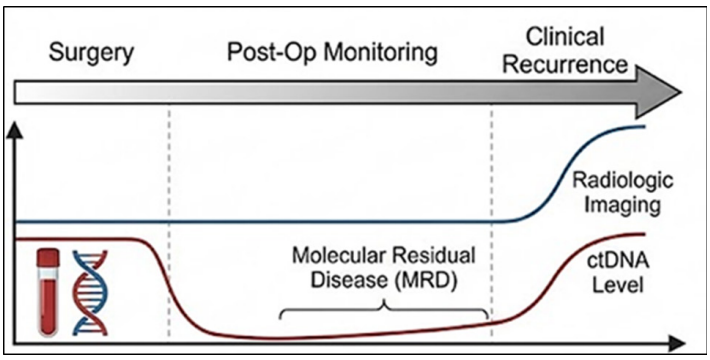

Figure 3: Liquid biopsy and molecular residual disease. Timeline backbone of post-treatment monitoring. ctDNA acts as a "molecular echo," detecting molecular residual disease (MRD) months before clinical or radiologic recurrence becomes visible.

Serial ctDNA analysis can reveal molecular residual disease after apparently curative treatment and may detect recurrence earlier than conventional imaging. The value of ctDNA also extends beyond simple relapse detection. When plasma variants are compared with the genomic profile of the original tumor, it may be possible to distinguish true recurrence from a second primary malignancy. Shared truncal mutations support clonal continuity, whereas clearly different mutational profiles may suggest an independent tumor arising in a previously altered tissue field [46-48]. This distinction can have direct clinical implications because it may affect treatment selection, surgical planning, and interpretation of risk.

At the same time, ctDNA analysis has important limitations. Plasma sequencing examines total cfDNA, not ctDNA in isolation, and this background pool includes DNA released from non-tumor cells. One of the main biological confounders is clonal hematopoiesis, an age-related expansion of hematopoietic clones carrying mutations in genes such as DNMT3A, TET2, and ASXL1 [40,49]. Because some of these variants overlap with genes also altered in solid tumors, mutations of hematopoietic origin may be misinterpreted as tumor-derived ctDNA, creating false-positive MRD results.

The importance of clonal hematopoiesis is not only technical. It has also been associated with later hematologic malignancy and with cardiovascular risk, suggesting that it reflects broader age-related genomic change [50]. In liquid biopsy interpretation, however, its main relevance is practical: results need to be read in context. Sequencing matched white blood cells alongside plasma can improve specificity by separating hematopoietic variants from true tumor-derived alterations [51]. Without that step, highly sensitive assays may detect age-related clonal expansion rather than residual cancer.

These issues highlight an important principle already emphasized in the earlier sections: no single modality is sufficient on its own. ctDNA provides a highly informative longitudinal signal, but its performance depends on tumor fraction, shedding biology, assay design, and clinical context. It is especially useful in the postoperative and MRD setting, where the genomic profile of the primary tumor is already known. Its role in primary screening is much less certain, because very early tumors may release little ctDNA and because signal interpretation becomes more difficult in low-prevalence settings [41,42].

Liquid biopsy therefore occupies a clear but limited place within the broader early-detection framework. Germline genetics helps define inherited risk. Somatic evolutionary analysis helps describe tissue conditioning and field change. ctDNA adds a time-based layer by tracking residual clonal activity over time. In this integrated view, liquid biopsy does not replace imaging or pathology, but complements them by identifying molecular events that may occur before structural recurrence becomes visible.

Colorectal Cancer and Volatile Organic Compound Analysis: Toward Continuous "Volatomics"

Among solid tumors, colorectal cancer (CRC) is of particular interest for early-detection research because it develops in direct contact with the gut lumen and its microbial and metabolic environment. Unlike tumors that arise in relatively sterile or less accessible sites, CRC develops within a biologically active compartment shaped by ongoing interactions among epithelial

cells, microbial communities, diet, and inflammatory signals. In this setting, volatile organic compounds (VOCs) may provide a functional readout of tumor-associated metabolic change, complementing the genomic information provided by mutational analysis and the longitudinal information provided by ctDNA.

The rationale for VOC-based detection comes from several converging observations. Colorectal tumorigenesis is associated with metabolic reprogramming, oxidative stress, and lipid peroxidation, while dysbiosis alters microbial fermentation and sulfur metabolism. Large microbiome studies have consistently shown enrichment of Fusobacterium nucleatum and other taxa in CRC tissue [52-54]. More recent work also suggests that early colorectal carcinogenesis includes stromal and tissue-level remodeling, with altered biomechanical features reported in early-onset CRC [55]. In parallel, metagenomic and metabolomic analyses have shown stage-related changes along the adenoma-to-carcinoma sequence, suggesting that microbial and metabolic shifts may occur before invasive disease develops [56]. Reduced butyrate and other short-chain fatty acid changes, together with broader alterations in microbial metabolites and inflammatory signaling, further support the idea of a metabolically altered field [57-59]. These changes can generate volatile metabolites that are measurable in feces, urine, or breath [60]. Early proof-of-concept studies showed that VOC profiling could distinguish CRC from controls by gas-analysis platforms [61,62]. More recent evidence includes a systematic review and meta-analysis reporting pooled sensitivity around 0.86 and specificity around 0.90 for fecal VOC-based CRC detection, as well as independent work on exhaled VOC discrimination [63,64]. Together, these findings support biological plausibility, although they do not yet establish routine clinical utility (Table 3).

From a mechanistic point of view, CRC-related VOC changes probably reflect combined host and microbial metabolism. Sulfur-containing compounds such as methyl mercaptan and dimethyl trisulfide may be linked to altered sulfur amino acid metabolism and to microbial hydrogen sulfide production, a pathway with documented genotoxic and redox-related effects [65-67]. Oxidative stress and lipid peroxidation may contribute aldehydes and ketones detectable in volatile profiles [63,68]. Microbial tryptophan metabolism can generate indolic compounds that influence epithelial and immune pathways, including signaling through the aryl hydrocarbon receptor [69,70]. In this sense, VOC profiles may be viewed as a metabolic extension of the broader tissue and luminal changes that accompany field conditioning in CRC.

Current VOC-based approaches, however, remain mostly cross-sectional. Fecal headspace analysis and breath testing capture a metabolic state at one point in time, and that state can be affected by diet, circadian variation, bowel transit, medications, and short-term microbiome fluctuation. These methods are therefore informative, but they remain episodic, much like the threshold-based approaches discussed in earlier sections [60].

The main idea proposed here is to consider a longitudinal alternative. Rather than searching for one specific "cancer gas," it may be more useful to assess whether CRC development produces a sustained shift in a composite volatile profile relative to a person's own baseline. In that model, the important signal would not be the isolated presence of one compound, but a repeated and stable change across a broader pattern of VOCs. This idea is consistent with the trajectory-based approach introduced in chapters 1–4, but it remains a hypothesis rather than an established clinical method.

Some technologies already suggest that more continuous gastrointestinal gas monitoring is technically possible. A wearable garment-based system has been reported for long-term monitoring of flatus-associated microbial gas production in ambulatory settings [71]. Ingestible and miniaturized sensor platforms also show that real-time assessment of luminal chemistry is feasible in principle [72,73]. At present, however, there is no validated clinical device that can continuously analyze intestinal gas composition in a comprehensive multi-analyte way for cancer surveillance. The idea discussed here should therefore be understood as a translational possibility based on current biological and technical developments, not as a tool ready for immediate clinical use.

A future platform of this kind would likely require a combination of sensing approaches rather than a single sensor. Broad VOC-responsive arrays, such as metal oxide semiconductor systems, and trace-detection approaches, such as acoustic-wave sensors, are already established in the sensing literature [74,75]. Repeated measurements obtained under standardized conditions could

Table 3: Biological rationale, current evidence, and translational status of VOC-based approaches in colorectal cancer.

Domain	Key observations	Clinical / biological implication	Main limitation
Microbiome changes	Enrichment of *Fusobacterium nucleatum* and other taxa in CRC	Supports a tumor-associated microbial ecosystem shift	Inter-individual variability
Metabolomic alterations	Reduced butyrate, altered sulfur and tryptophan metabolism, oxidative stress products	Suggests functional biochemical remodeling along the adenoma–carcinoma sequence	Limited specificity
VOC detection studies	Fecal and breath VOC profiles can discriminate CRC from controls in proof-of-concept studies	Supports non-invasive detection potential	Mostly cross-sectional and heterogeneous
Sensor technologies	Wearable, ingestible, and miniaturized chemical sensing is technically feasible	Suggests future potential for repeated monitoring	No validated oncologic multi-gas platform yet
Longitudinal volatomics concept	Persistent deviation from individual baseline may be more informative than single time-point sampling	Fits trajectory-based surveillance model	Still hypothetical; requires prospective validation

further improve interpretability by helping distinguish persistent changes in composite volatile profiles from ordinary physiological variability.

This approach is consistent with the general hypothesis proposed here. Germline information helps define inherited risk, somatic evolution and field cancerization describe how tissues change over time, and ctDNA adds a molecular signal of residual clonal activity. Continuous volatile profiling, if it becomes technically reliable and clinically validated, could provide an additional layer by capturing metabolic changes within a biologically altered colorectal field. In this sense, volatomics would not replace colonoscopy, FIT, imaging, or molecular assays, but could eventually serve as a non-invasive longitudinal surveillance layer that supports risk stratification and helps trigger further diagnostic evaluation when sustained metabolic deviations are detected.

This framework remains exploratory. Before any clinical application, prospective studies would need to define sensitivity, specificity, predictive value, and robustness against major confounders, including diet, antibiotics, inflammatory bowel disease, and inter-individual microbiome variation. Standardization of sampling, sensor calibration, and analytic pipelines would also be essential. Even so, the convergence of microbiome research, metabolomics, and sensor technology makes the idea of continuous metabolic monitoring in CRC biologically plausible and worth further study [60,71,73].

CRC therefore offers a useful model in which tumor biology, microbial ecology, and metabolomic output can be studied together (Figure 4). Although a multi-gas volatomic device for oncologic use does not yet exist, the concept follows logically from several existing lines of evidence. If validated in prospective settings, such an approach could add a dynamic and non-invasive triage layer to CRC surveillance by identifying sustained metabolic changes that justify prioritized diagnostic assessment.

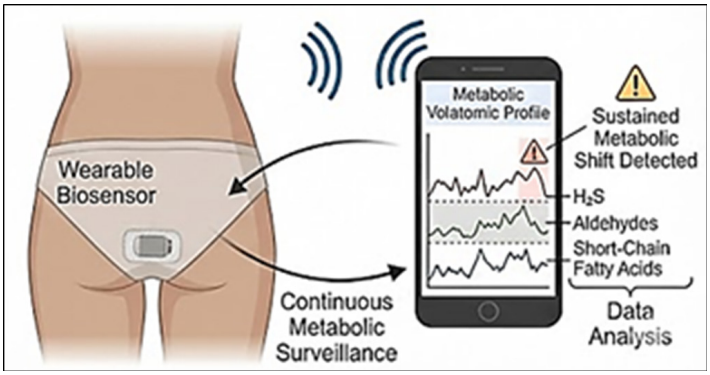

Figure 4: Concept of longitudinal volatile profiling in colorectal cancer. This figure illustrates a proposed future framework in which repeated volatile measurements are interpreted against an individual baseline. The model is hypothesis-driven and intended as a triage concept, not as a substitute for established diagnostic methods.

Toward Integrated Early Detection Platforms

The previous sections have described several different dimensions of early detection: longitudinal biomarker monitoring, inherited susceptibility, somatic field change, molecular residual disease, and metabolic alterations linked to tissue and microbiome remodeling. The main point of this manuscript is that future progress is unlikely to come from further refinement of only one of these approaches. A more realistic direction is integration. In that setting, early detection is better understood as a longitudinal decision process rather than as a single test.

One of the main limits of conventional screening is that it often relies on isolated measurements interpreted against population-based thresholds. In laboratory medicine, this problem has long been recognized through the concept of the reference change value (RCV), which helps define when serial measurements in the same person exceed expected analytical and biological variation [76,77]. Personalized reference intervals extend this idea by defining an individual's expected range on the basis of repeated measurements over time [78,79]. Longitudinal multi-omics studies support this logic, showing that many molecular features remain relatively stable within an individual while differing substantially across individuals [80,81]. This pattern strongly supports baseline-based interpretation rather than reliance on one-time thresholds.

Within this type of platform, biomarker mapping early in adult life would not function as a stand-alone cancer test. Its main purpose would be calibration. Repeated measurements could help define the usual background variation against which later changes are judged. This becomes more informative when combined with germline risk information. High-penetrance variants, such as those in BRCA1/2 or Lynch-associated genes, can justify earlier and more intensive surveillance. At the population level, polygenic risk scores (PRS) may further refine stratification by identifying subgroups in whom more intensive screening might be more informative [24,25]. More recent implementation studies suggest that PRS-guided screening is feasible, but also show that real-world use raises practical and equity-related challenges [82,83].

In individuals without a prior cancer diagnosis, early detection can be viewed as longitudinal risk calibration rather than one-time screening. Germline risk, repeated biomarker measurements, and evidence of early tissue or metabolic change may together inform decisions about escalation to imaging, endoscopy, or biopsy. The proposed volatile-monitoring layer remains hypothetical and would require prospective validation.

In this framework, germline information does not simply divide people into hereditary and non-hereditary groups. It acts more usefully as a prior risk factor that changes how later signals are interpreted. A small biomarker shift, a low-level ctDNA signal, or a subtle metabolic abnormality may carry different significance in a high-risk individual than in someone at average inherited risk. Integration therefore improves interpretation, not just data collection (Figure 5).

Table 4: Comparative evaluation of major early-detection modalities. The table highlights the principal strengths, main limitations, current evidence base, and degree of clinical readiness of the different methods.

Modality	Main strengths	Main limitations	Current evidence base	Current clinical status
Germline genomics	Identifies inherited susceptibility; informs long-term risk stratification and surveillance	Does not detect active cancer; limited mainly to risk assessment rather than lesion detection	Strong for hereditary risk assessment	Established in selected hereditary cancer settings
Field cancerization	Captures early tissue-level and premalignant changes; reflects local biological context	Lack of standardized biomarkers and limited routine clinical applicability	Moderate, mainly mechanistic and translational	Developing
Circulating tumor DNA (ctDNA)	Useful for molecular residual disease assessment and recurrence monitoring; high specificity in tumor-informed settings	Limited sensitivity in very early-stage disease and low-shedding tumors; possible confounding by clonal hematopoiesis	Strong in MRD and recurrence settings	High in selected post-treatment settings, not established for general population screening
Volatile organic compounds (VOCs)	Non-invasive sampling; may reflect metabolic and microbiome-related changes	High biological and technical variability; limited standardization; mostly exploratory	Preliminary to moderate	Emerging

The framework becomes even more informative after a first tumor has occurred. Molecular profiling of the primary tumor can define a patient-specific template containing driver mutations, mutational signatures, and repair defects [30]. This information may guide treatment in the short term, but it can also support later surveillance. Tumor-informed ctDNA assays can monitor recurrence with high specificity [43], and comparative genomic analysis may help distinguish recurrent disease from a second primary tumor with a different clonal origin [46]. In that sense, a prior cancer becomes an important source of information for more precise follow-up.

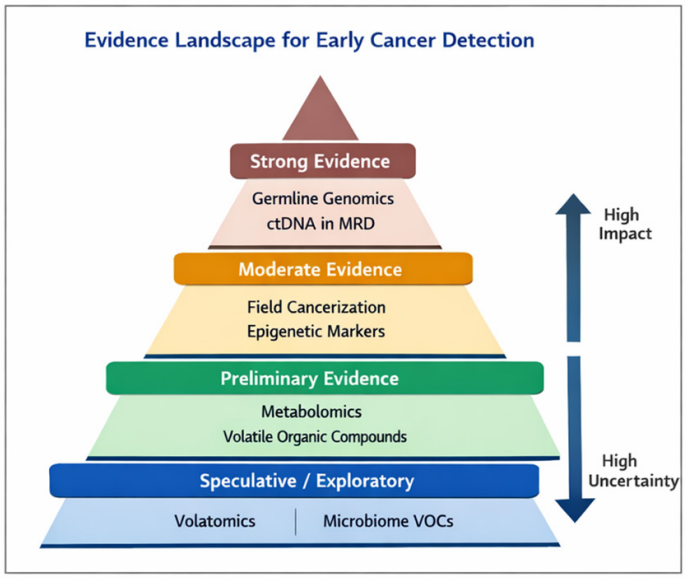

Figure 5: Evidence landscape for integrated early cancer detection. Schematic ranking of current evidence across major components of early-detection research, from more established areas to exploratory domains. The figure highlights that germline genomics and ctDNA in molecular residual disease are supported by stronger current evidence, whereas metabolomics, VOC-based approaches, and especially continuous volatomics remain more preliminary and require prospective validation. The figure is conceptual and does not imply equal performance across cancer types or assay platforms.

After treatment of a primary malignancy, surveillance can incorporate the molecular profile of the original tumor. Tumor-informed ctDNA monitoring may help detect recurrence, while comparison of genomic profiles may help distinguish clonal relapse from a second primary tumor.

Liquid biopsy, especially in the setting of molecular residual disease, fits naturally into this integrated model because it provides repeated molecular assessment over time. However, as discussed in the previous section, its interpretation depends on context. Technical limitations, low tumor fraction, and confounding from clonal hematopoiesis can all affect results [5,84]. For that reason, ctDNA should not be presented as a universal early-detection solution. Its main strength is that it adds a time-based signal of clonal activity that can complement other forms of information rather than replace them.

The volatomics concept introduced in the CRC section adds a different type of signal. If continuous or repeated metabolic sensing becomes technically reliable and clinically validated, it could provide information on functional ecosystem changes that may occur before clear structural disease is visible. This potential role should be framed cautiously. It would be a triage layer rather than a replacement for colonoscopy, imaging, or tissue diagnosis. Current ingestible and miniaturized chemical sensing technologies show that gastrointestinal monitoring is technically possible in principle [72,73], but the step from technical feasibility to validated oncologic use remains substantial.

Bringing these data streams together would require robust computational methods. Multi-omics machine-learning approaches in oncology are promising, but their usefulness depends not only on model complexity, but also on appropriate integration strategy, careful validation, and clinically interpretable outputs [85,86]. For clinical use, an integrated platform would need to generate understandable risk estimates linked to clear escalation pathways, not just opaque binary outputs. Clinical trust depends on interpretability as much as on predictive accuracy.

Taken together, these components suggest a layered model of early detection. Longitudinal biomarker mapping helps define individual reference stability. Germline data provide inherited risk context. Tumor molecular profiling adds lineage-specific information after diagnosis. ctDNA adds temporal resolution for residual or recurrent disease. Metabolic sensing, if validated, could provide another non-invasive layer reflecting functional biological change. No single element is sufficient on its own, but their combination may allow more careful and biologically informed surveillance than age-based screening alone.

The main translational challenge is now to determine which combinations of these layers improve outcomes in practice, in which settings, and at what cost. This will require prospective validation, clear definitions of action thresholds, and careful attention to false positives, overdiagnosis, and uneven access [43,82]. Integration should therefore be gradual and evidence-based. If that is achieved, early detection could move away from sporadic screening toward a more adaptive system in which surveillance intensity is matched more closely to biological risk and clinical context.

Challenges and Ethical Considerations

The possible value of integrated early-detection platforms must be considered together with their ethical, clinical, and social implications. As screening becomes more sensitive, more frequent, and more complex, the key question is no longer only whether earlier detection is technically possible, but whether it leads to an overall clinical benefit. Greater sensitivity is not automatically beneficial if it also increases overdiagnosis, anxiety, unnecessary procedures, inequitable access, or pressure on healthcare systems. For that reason, technical progress needs to be matched by careful clinical judgment.

One of the main risks is overdiagnosis. This does not simply reflect a statistical problem, but also the biological fact that some lesions detected by screening may never progress to symptomatic or life-threatening disease during a person's lifetime [87,88]. As detection moves earlier, including toward pre-neoplastic states or weak molecular signals of uncertain meaning, the boundary between useful early intervention and unnecessary medicalization becomes less clear. Multi-marker assays, ctDNA monitoring, and future metabolic sensing platforms may all produce low-level or indeterminate findings whose natural history is not well understood. Without clearly defined follow-up pathways, such findings may expose otherwise healthy people to repeated tests, invasive procedures, and overtreatment.

The psychological effects of intensified monitoring also need to be taken seriously. Systematic reviews suggest that, at the population level, anxiety related to screening is often limited and short-lived. However, some individuals, especially those with false-positive results or prolonged uncertainty, may experience more persistent distress [89]. In a longitudinal monitoring model, communication of risk becomes part of clinical care itself. Clear explanation of uncertainty, careful presentation of probabilities, and structured follow-up are not optional extras; they are necessary parts of responsible implementation [90].

Highly sensitive assays create another challenge: they can detect signals that are biologically real but clinically misleading. False-positive results may arise from analytical variation, benign inflammation, or age-related clonal processes such as clonal hematopoiesis. As discussed earlier, clonal hematopoiesis can complicate plasma-based genomic testing and may lead to unnecessary downstream investigation if not properly recognized [91]. Even assays with high analytical specificity may still create substantial diagnostic workload when used in low-prevalence populations. Ethical analyses of multi-cancer early detection (MCED) testing have therefore emphasized that clinical utility cannot be judged only by test performance. It must also include the consequences of follow-up testing, use of healthcare resources, and the burden placed on patients and health systems [92,93]. In this setting, a positive result should be treated as a triage signal rather than as a diagnosis, and it should trigger predefined, evidence-based next steps.

Economic questions are equally important. Long-term monitoring that includes genomic profiling, repeated molecular assays, and possibly wearable sensing could be costly, and its cost-effectiveness is likely to depend heavily on disease prevalence, test performance, and the intensity of downstream management. Modeling studies suggest that MCED approaches may have favorable value under some assumptions, but the results are highly sensitive to how those assumptions are set [94,95]. There is also an important question of fairness. If more advanced detection technologies become available mainly to wealthier groups through subscription-like or concierge models, they could widen existing inequalities in cancer outcomes rather than reduce them. For that reason, implementation should be gradual and supported by strong evidence.

Continuous sensing technologies add further concerns related to privacy and data governance. Wearable and ingestible devices can generate large amounts of detailed physiological information, which creates risks related to re-identification, cybersecurity, and data use beyond the original clinical purpose [96,97]. In the case of volatile or gastrointestinal monitoring, the information collected may be especially sensitive and potentially stigmatizing. Responsible development would therefore require data minimization, secure storage, transparent consent procedures, and a clear distinction between clinical care and research use [96,98]. Trust is likely to be essential for patient acceptance.

At a broader level, the ethical problem of integrated early detection is how to balance possible benefit against expanding medicalization. A longitudinal and multi-layered surveillance model may improve risk assessment, but it may also normalize constant monitoring and widen the category of people considered to be in a pre-disease state. Ethical analyses of early detection repeatedly identify uncertainty, autonomy, privacy, justice, and proportionality as central concerns [90]. The goal should not be to detect as much as possible, but to

achieve the greatest overall benefit with the least unnecessary harm.

For integrated platforms to become part of routine care, they should be held to standards similar to those applied to new therapeutic strategies. This means prospective evaluation, clear reporting of false-positive pathways, clinically meaningful endpoints, and explicit planning for fair implementation [92,98]. Early detection should protect patients not only from advanced cancer, but also from the harms that can arise when abnormal signals are found before there is enough evidence to act on them appropriately. In this sense, ethical rigor is not an obstacle to innovation. It is what makes innovation clinically responsible. The more powerful and sensitive early-detection technologies become, the more important careful governance will be.

Conclusion

Early cancer detection is moving beyond a model based only on population thresholds, episodic testing, and identification of structural lesions. That model has reduced mortality in selected cancers, but it usually detects disease only after biological changes have become large enough to be anatomically, biochemically, or radiologically visible. The main argument of this manuscript is that further progress is unlikely to come from one single test. It is more likely to come from combining several types of information and interpreting them over time within the same individual.

Cancer develops over years through the interaction of inherited susceptibility, somatic mutation, clonal expansion, tissue remodeling, and metabolic change. Germline variants help define long-term risk. Somatic evolution and field cancerization describe changes in tissue before overt malignancy appears. After a tumor has developed, its molecular profile can help guide follow-up through ctDNA-based monitoring. Emerging metabolomic approaches suggest that functional biological changes may also be detectable before structural disease becomes clear. Each of these approaches captures a different part of the process.

The value of the framework proposed here lies not in any one component alone, but in the possibility of combining them in a clinically meaningful way. Longitudinal biomarker assessment may help define personal baselines. Germline information may help place later findings in a risk context. Tumor-informed molecular profiling may improve interpretation of recurrence and second primary disease. ctDNA may provide a time-based signal of residual clonal activity. The proposed volatomics layer remains hypothetical, but it offers an example of how future metabolic monitoring might add another non-invasive dimension if it can be technically validated and clinically standardized. This integrated approach is not intended to replace established methods such as colonoscopy, mammography, or low-dose CT. Its more realistic role would be to support risk stratification and triage. In that model, emerging biological signals would not be treated as diagnoses in themselves, but as findings that help decide when further diagnostic evaluation is warranted. The emphasis would shift from age alone to a combination of inherited risk, biological change over time, and clinical context.

Any move in this direction will require careful validation. Prospective studies, transparent reporting of false-positive pathways, clear action thresholds, equitable access, and strong ethical safeguards will all be necessary. Greater sensitivity is not enough on its own. The important question is whether earlier and more complex detection strategies improve outcomes without causing excessive overdiagnosis, anxiety, unnecessary procedures, or widening disparities in care.

If these conditions are met, integrated longitudinal detection could help move oncology toward a more adaptive model of surveillance. In that setting, early detection would be understood less as the discovery of a lesion at one moment in time and more as the recognition of meaningful biological change across time. The goal would not be maximal detection, but earlier and more useful detection in settings where intervention can genuinely improve patient outcomes.

In this evolving landscape, early detection becomes less a single moment of discovery and more an ongoing process of interpretation.

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