Supplemental Table 1. Examples of potential biological and technical pitfalls for ctDNA assays

Consideration	Pitfalls	Potential solutions
Biological		
ctDNA assays have an appreciable rate of discordance with tumour testing.	Cases where a mutation is not detected may be interpreted as the variant not being present in the tumour, when in actuality, there was insufficient ctDNA in the specimen.	1. Report communicates the potential for discordance in such cases. 2. Terms such as *non-informative* or *not detected* are used in report language. 3. Future research focused on measurement of ctDNA purity in specimen and ability to differentiate whether variant is not present in tumour versus insufficient ctDNA.
Potential germline variant identified by ctDNA assay.	1. Failure to identify an unknown germline heritable cancer predisposition variant could impact treatment and other management decisions for both the patient and family members. 2. Incorrectly attributing a variant with a high VAF as having a somatic origin could confound interpretation of the ctDNA assay.	1. Analyses, follow-up testing, patient counselling, and reporting of potential germline variants should generally follow ESMO recommendations for germline-focused analysis of tumour-only sequencing [45]. 2. Potential pathogenic germline variants in genes associated with heritable cancer predisposition should be flagged with an alert for the clinician. 3. In most cases, follow-up clinical testing should be performed to determine if variant is germline or somatic. 4. Future research focused on ctDNA features that could differentiate germline versus somatic origin of variant.

Clonal haematopoiesis is a common challenge for assays that include genes implicated in clonal haematopoiesis.	Variant identified in ctDNA assay is assumed to be present in the tumour but is actually derived from leukocytes.	1. Report communicates the potential non-tumour origin of variants in genes commonly implicated in CHIP. 2. Assays incorporate sequencing of leukocytes in addition to plasma DNA. 3. Future research focused on identification of mutations derived from clonal haematopoiesis. 4. Future research focused on interpretation and reporting of CHIP with respect to risk of haematologic malignancy, cardiovascular disease, or outcomes in advanced cancers.
Benign lesions can contain oncogenic variants.	Identification of an oncogenic variant in ctDNA assays is not diagnostic of malignancy. As an example, *BRAF* V600E variant has been identified in plasma DNA from individuals with benign nevi [122].	Interpretation of ctDNA assays should be done in the context of tissue studies and other clinical information.
Technical		
Assays are validated to detect and report specific types of variants (e.g., SNVs, small insertions/deletions, amplifications/copy number losses, gene fusions).	A ctDNA assay that detects SNVs and small insertions or deletions will not report on amplifications/copy number losses, gene fusions.	Report communicates which variant types are reported.

Some variant types are more difficult to detect with ctDNA assays.	1. In tissue-based testing, RNA-based assays are being increasingly used for detection of gene fusions and splicing variants (e.g., *AR* splice variants). These variants may be detected at a lower frequency in ctDNA studies, even with sufficient ctDNA. 2. Variants involving LOH as well as low level copy-number gains or losses are technically more difficult to detect in ctDNA assays. 3. Genomic tumor features such as TMB, MSI, HRD are an evolving area and plasma-based measurements should not routinely be used in place of validated tissue-based assays.	1. Report communicates individual performance of different variant types. 2. Future research focused on improved detection of challenging variant types. 3. Future research on analytical and clinical validity of plasma-based genomic measurements.
Analytical sensitivity of assays vary significantly and may be influenced by amount of input DNA. It is likely that different intended uses of ctDNA will have different analytical sensitivity requirements.	Use of an expanded NGS-based ctDNA assay designed for genotyping in advanced cancers may not provide sufficient sensitivity for early-stage cancer MRD.	1. Analytical sensitivity of assay is reported. 2. In cases where input plasma DNA is limiting, the reported sensitivity is adjusted or a warning is inserted in the report. 3. Future research into required assay sensitivity for given indications.

Abbreviations: ctDNA – circulating tumour DNA; plasma DNA – cell-free DNA extracted from plasma; CHIP – clonal haematopoiesis of indeterminate potential; SNVs – single nucleotide variants; MSI – microsatellite instability; TMB – tumour mutation burden; LOH – loss of heterozygosity; HRD – homologous recombination deficiency.