Highlights, general discussion and future perspectives
Chapter 10

HIGHLIGHTS

1. Recommendations from the UMCG Molecular Tumor Board were highly adhered to and resulted in a positive clinical response in the majority of patients with advanced non-small cell lung cancer (chapter 2).

2. Molecular Tumor Boards associated with tertiary cancer referral centers in the Netherlands were similar in setup and highly agreed in targeted therapy recommendations. The “Dutch MTB model” can form the backbone of a national quality guideline regarding Molecular Tumor Boards (chapter 3).

3. A high inter-laboratory concordance in the classification of pathogenicity by Dutch pathology laboratories was demonstrated in spite of a potentially subjective and varying manual approach to interpret challenging variants. A seven-step approach for critical assessment of evidence of pathogenicity and actionability was presented (chapter 4).

4. In patients tested for the presence of NTRK1–3 fusions in routine diagnostics, the sensitivity of pan-TRK immunohistochemistry was insufficient. Therefore, the utility of pan-TRK immunohistochemistry as a prescreening tool should be reconsidered (chapter 5).

5. A rare case of non-small cell lung cancer mixed with chronic myelomonocytic leukemia recognized in a single tissue biopsy demonstrated that the presence of a seemingly unexpected oncogenic mutation should prompt the consideration of a second malignancy (chapter 6).

6. Appropriately classified 'uncommon, actionable' EGFR mutations are predictive for similar overall survival duration upon treatment with targeted therapy compared to patients with EGFR L858R mutations in non-small cell lung cancer (chapter 7).

7. ALK fusion-positive non-small cell lung cancer patients with on-target resistance mutations benefit from sequential ALK inhibition, with likelihood of benefit depending on the specific combination of mutation and inhibitor (chapter 8).

8. Triplet EGFR/BRAF/MEK inhibition is a viable treatment option in non-small cell lung cancer patients with osimertinib-induced BRAF V600E mutation, which deserves further exploration (chapter 9).
GENERAL DISCUSSION

The aim of this thesis was to investigate decision-making strategies used to reach a diagnostic or therapeutic recommendation upon detection of rare somatic variants in routine cancer care. Molecular testing results are becoming increasingly complex and require a structured approach in order to be translated into an appropriate diagnostic or therapeutic recommendation. MTBs play a central role in this process. In this chapter, the main findings of this thesis as well as work published in literature are used to provide a framework for a recommended optimal decision-making route for the current clinical setting. In addition, recent advances in molecular pathology that can affect these strategies in the future are discussed.

The findings in this thesis are relevant for selecting patients and techniques for testing (rare) molecular markers, the optimal interpretation of rare results from molecular diagnostic tests in pathology, appropriate reporting of such molecular results for clinicians, achieving a treatment decision in case of rare alterations, and establishing the role of MTBs in oncology. Each of these aspects will be discussed chronologically – from diagnosis to treatment.

Selecting the appropriate technique to test for molecular markers

Molecular diagnostic analysis has become indispensable in the testing landscape of pathology. The number of patients requiring diagnostic, prognostic and predictive molecular testing for routine clinical purposes is continuously increasing.\(^1,2\) As a consequence, molecular pathology is among the fastest developing subspecialties of pathology: new DNA- and RNA-based technologies are rapidly introduced, and an increasing extent of the genome can be mapped in routine diagnostics. Molecular diagnostic techniques are stand-alone or used in sequence as a diagnostic or predictive algorithm. The efficacy of these algorithms is determined by a variety of factors such as turnaround time, reliability of individual tests, their costs and reimbursement.

The non-molecular technique IHC is cheaper and faster than molecular techniques. When the reliability of IHC is equal or superior to a comprehensive molecular test, this technique should be preferred. For example, IHC has proven equally reliable as molecular tests such as fluorescent in-situ hybridization (FISH) and next-generation sequencing (NGS) to demonstrate MDM2 amplification as a marker for (dedifferentiated) liposarcoma and atypical lipomatous tumors.\(^3\) On the contrary, a poor association was found between IHC and molecular tests to determine the presence of MET amplification or MET exon 14 skipping in NSCLC, and thus, molecular tests are preferred to detect these alterations.\(^4\) These diagnostic algorithms should be evaluated when experience builds or novel techniques become available, especially when the marker is rare. A similar evaluation was performed...
in chapter 5, which demonstrated that IHC, which had previously been recommended as a screening tool to exclude the prevalence of rare NTRK fusions,\textsuperscript{5,6} in fact had a low sensitivity when used in routine practice. For some types of cancer, however, it may not be cost-effective to test all patients for a molecular marker using a costly RNA-based technique if less than 1% actually harbor the alteration. In these patients, it could suffice to preselect patients based on other, more common markers. For example, in colorectal cancer, approximately 0.25% of patients harbor NTRK fusions, but 89% of all NTRK fusion-positive patients are mismatch repair deficient (MMRd) and do not harbor BRAF mutations (BRAFwt).\textsuperscript{7} When testing only MMRd/BRAFwt colorectal cancer patients, the prevalence of NTRK fusions increases to 5.3%; thus, it could be feasible to only test NTRK with an RNA-based test in MMRd/BRAFwt patients. On the contrary, for patients who are already tested with gene panels, additional markers can often be included in the assay. NSCLC patients, for example, are routinely tested for fusions in ALK, RET, ROS1 and MET exon 14 skipping in a single RNA-based assay that can often easily be expanded with the much rarer NRG1 and NTRK1–3 fusions (both <1% prevalence). Ultimately, the best way to confirm that a predictive test is reliable is when a positive test associates with response to therapy. An example is testing ALK fusions in NSCLC: prior to the introduction of RNA testing, these were often demonstrated using FISH. However, a positive IHC turned out to be a better predictor of response, with FISH-negative but IHC-positive patients still responding to targeted ALK inhibition.\textsuperscript{8} Thus, the utility of IHC to replace or complement molecular techniques differs by each molecular marker that is being tested for.

In summary, the optimization of molecular-guided decision-making starts with selecting the right (sequence of) techniques for detecting molecular markers. This needs to be determined for each individual marker based on its prevalence in a cancer type, its association with response, its co-occurrence with other alterations and, if applicable, the ease of integrating the marker into existing gene panels to increase cost-effectiveness. For rare NTRK fusions, IHC with currently validated antibodies was demonstrated to have insufficient sensitivity as a preselection tool. An up-front RNA analysis is preferred when possible. Otherwise, standardized scoring criteria as well as more sensitive pan-TRK antibodies are needed.

**Interpretation and reporting of rare somatic variants in routine diagnostics**

In the Netherlands and other European countries, the interpretation and reporting of molecular diagnostic results is the responsibility of dedicated scientists with ample experience in molecular pathology – the CSMPs.\textsuperscript{9} The Dutch Society for Pathology (NVVP) has been running an educational program for CSMPs since 2014, and practicing CSMPs adhere to strict quality assurance guidelines.\textsuperscript{10} Pathologists are responsible for the final pathology report, and the final reporting to the requesting physician is therefore a shared
collaborative effort between CSMPs and pathologists. In the interpretation of rare somatic variants, two considerations are crucial: the pathogenicity and the actionability of a variant. The assessment of actionability will be discussed in part II of this general discussion.

**Assessing the pathogenicity of a somatic variant**

The pathogenicity of a variant is determined by its disease-causing capacity. In cancer, a variant is pathogenic when it is known to contribute to malignant transformation. Pathogenicity is classified using an adapted version of the 2015 ACMG/AMP guidelines, which proposed a five-tier scheme (pathogenic – likely pathogenic – variant of unknown or uncertain clinical significance (VUS) – likely benign – benign). Pathogenicity is universal: for example, a \textit{BRAF} V600 mutation is universally transforming in cell cultures and drives a variety of tumors.

There is no (inter)national consensus on how the interpretation of pathogenicity should be performed. Classification systems for pathogenicity have been standardized for germline variants (in tumor suppressor genes), but these systems provide limited guidance with respect to classification of pathogenicity of somatic variants in oncogenes. Adapted criteria for somatic variants have been proposed by the Belgian ComPerMed network, and more recently, by the French SoVaD network, but these workflows have not been adopted by laboratories in the Netherlands. Chapter 4 demonstrated that Dutch CSMPs' individual strategies for variant interpretation were largely subjective and manual, but that they nevertheless achieved a high inter-laboratory agreement in classifying pathogenicity of variants. With the growing number of markers and sequencing of whole genes, more rare somatic variants are found. In effect, the CSMPs' responsibilities in routine diagnostics are becoming more challenging and time-consuming. Automated prediction tools for pathogenicity as well as commercially available decision-making tools for actionability are therefore a welcome development. However, the currently available tools are highly variable in terms of performance and show major discrepancies. Therefore, for the time being, the interpretation of rare somatic variants remains a manual process, in which CSMPs screen data- and knowledge bases for relevant evidence. Based on the results in chapter 4, a manual approach was recommended, but this approach relies on a subjective weighing of arguments. Improvement of the inter-laboratory agreement in classifying pathogenicity can be achieved by standardizing this procedure. A reliability comparison between the standardized scoring systems proposed by the Belgian ComPerMed and the French SoVaD networks is needed, and if either improves the inter-laboratory agreement, (inter)national adoption will be warranted.
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Reporting of somatic variants in a pathology report

CSMPs bear responsibility for the decision whether or not to report a detected variant in the pathology report. National guidelines for the reporting of detected variants have been in place since 2012, and are continuously in development to accommodate novel techniques and molecular markers. Chapter 4 showed that variants are reported back to the clinic when they are classified as pathogenic or likely pathogenic, and not reported when they are classified as benign or likely benign. However, Dutch laboratories varied in their reporting of VUS: two laboratories structurally did not report VUS, whereas the remaining six did. The discussion on whether or not to report VUS is not new, and has been heated in clinical genetics. One argument to report VUS is that variants that have no known significance today may be reclassified in the (near) future, which could have clinical consequences for individual patients. The major argument against reporting VUS is that treating clinicians may interpret these VUS as pathogenic and unduly act upon it. For example, in chapter 7, it became apparent that in the Dutch population of NSCLC patients between 2013 and 2017, at least 16 NSCLC patients with a VUS in \( EGFR \) (26% of all reported \( EGFR \) VUS) had been treated – to no avail – with an EGFR inhibitor. In addition, considering the majority of variants that are detected in cancer tissue are classified as VUS, an increase in the genomic region sequenced in routine diagnostics would lead to an excess of variants that are included in the pathology reports. Considering the ongoing incorporation of large-panel sequencing methods such TruSight Oncology 500 (TSO-500; Illumina, San Diego, CA) and whole-genome sequencing (WGS) into routine diagnostics, reporting VUS in pathology reports will therefore be impractical in the near future. A different option would be to share all detected variants among other experts to ensure they are readily accessible for reclassification if necessary. A similar data-sharing initiative is already in place in Dutch Clinical Genetics departments.

In summary, although CSMPs in the Netherlands reach a high agreement in classifying pathogenicity, they rely on a manual approach with subjective weighing of arguments for pathogenicity. Introducing standardized scoring systems, such as those proposed by the Belgian ComPerMed and the French SoVaD networks, may improve the inter-rater reliability. In addition, the clinical course of patients may be affected by apparent differences in their reporting of rare or unknown variants, especially VUS. Nationwide harmonization of reporting criteria is therefore necessary, and considering reporting of VUS will likely be impractical with the increasing use of broad-panel sequencing methods, excluding them from pathology reports is preferable.
Diagnostic consequences of predictive molecular testing

In a variety of cancers, molecular diagnostics are used to test for diagnostic molecular markers. Examples are MDM2 amplifications in adipocytic tumors,\textsuperscript{23} 1p/19q co-deletions and IDH1/IDH2 mutations in adult-type diffuse gliomas,\textsuperscript{24} and various specific gene fusion in soft tissue or bone tumors.\textsuperscript{25} These markers are valuable additions to pathologists’ toolsets in determining a diagnosis and requesting these tests is at their discretion. Rare somatic variants detected for predictive purposes at the request of an oncologist may also serve a diagnostic purpose.

Challenging or complementing the initial diagnosis

Although uncommon, the initial diagnosis may be challenged when molecular testing reveals an unexpected molecular signature. An example is proffered by a report that showed that six squamous cell carcinomas that were considered lung primaries on the basis of the initial clinical presentation, whereas sequencing showed elevated tumor mutational burden (TMB) and UV-associated mutational signatures that suggested a primary origin from the skin, which was confirmed clinically.\textsuperscript{26} A mutation analysis can also point in the direction of a diagnosis when clinical and histological assessment cannot distinguish the origin. In a small subset of patients, molecular diagnostics can thus coincidentally complement the pathologists’ toolset of IHC stains, especially when these do not unambiguously demonstrate the diagnosis.

Revealing the presence of a second primary tumor of similar histology

A rare somatic variant may also herald the presence of a second primary tumor. This is true in patients with metastatic disease, who may harbor multiple lesions in the same site, especially in the lungs. When such patients are treated with systemic treatment, including targeted therapies, one of these lesions can show a response whereas the other does not. In this case, the two lesions show similar histology, but may both have developed independently and thus harbor different activating mutations. This has been reported before: Vaz et al. found two unique EGFR exon 19 deletions in separate lung adenocarcinoma biopsies, four years apart (after curative surgery of the first tumor), indicative of two independent primary tumors rather than a (metastatic) recurrence, which impacts decision-making.\textsuperscript{27} Lee et al. described multiple similar patients, including one with three (molecularly) unique primary tumors of the lung.\textsuperscript{28} In effect, predictive molecular testing may elucidate that a seemingly progressive lesion is in fact a second primary, possibly unmetastasized tumor that may be excised or irradiated without affecting the clinical course of the first primary tumor. These examples show the need for a proper clinicopathological assessment when
molecular diagnostics detect an unexpected somatic variant. Concurrent sequencing of frequently altered tumor suppressor genes (such as TP53 or CDKN2A) to demonstrate a clonal relationship could further facilitate this assessment.

Uncovering a co-existing (hematopoietic) disease
A third consideration that may emerge from the detection of rare somatic variants is that there is admixture of two populations of cells with unique mutations. Unlike IHC, most molecular diagnostic techniques are not spatial. In other words, a somatic variant cannot be traced back to the individual cell; rather, somatic mutations from any cell within a (macrodissected) biopsy will be tested, including cells that do not belong to the targeted cancer tissue. Chapter 6 illustrated that admixture with a second (hematological) malignancy in a tissue biopsy is possible. Although this is a rare case, admixture with non- or pre-malignant hematopoietic cells is not unlikely, as these cells can permeate any tissue biopsy. Lee et al. demonstrated that a JAK2 p.(V617F) mutation (frequent in polycythemia vera (PV), essential thrombocytopenia and primary myelofibrosis)\textsuperscript{29} that was detected in a duodenal carcinoma, in fact originated from PV.\textsuperscript{30} Furthermore, hematopoietic progenitor cells are known to acquire somatic mutations during human ageing without directly leading to cancer, a process known as clonal hematopoiesis of indeterminate potential (CHIP).\textsuperscript{31} This is an age-related precursor of hematological cancer, especially myeloproliferative neoplasms (MPN).\textsuperscript{32} As much as 5.2\% of patients are at risk of having a CHIP-associated mutations erroneously called as derived from a tumor.\textsuperscript{33} This was found to be true for much as 4\% of all TP53 mutations found in cancer biopsies.\textsuperscript{34} This risk is further increased when analyzing cell-free DNA: in NSCLC patients, CHIP-related mutations can be detected in 44.9\% of patients.\textsuperscript{35}

Genes that are commonly mutated in CHIP include ASXL1, ATM, CBL, CDKN2C, CHEK2, DNMT3A, EP300, HNF1A, IDH2, JAK2, MYD88, SF3B1, TET2, TP53, and U2AF1.\textsuperscript{34,36} As several of these genes can also be mutated in solid cancers (IDH2, JAK2, ATM, CHEK2 and TP53),\textsuperscript{17} the misinterpretation of these mutations can have therapeutic consequences. For example, mutations in ATM and CHEK2 are predictive markers for treatment with PARP inhibitors,\textsuperscript{38,39} JAK2 mutations are predictive markers for resistance to PD-1 blockade,\textsuperscript{40} and TP53 mutations are prognostic molecular markers for reduced survival in EGFR-mutant patients.\textsuperscript{41} When mutations in these genes are found in cancer tissue, this should prompt an investigation to exclude the possibility of a co-existing MPN, especially if the patient is older and the variant allele frequency of the CHIP-associated variant is relatively low compared to other detected variants.\textsuperscript{42} The mutations should always be considered with regards to the clinical, histological and immunohistochemical characteristics, and can therefore prompt clinicopathological discussion within an MTB. The management strategies proposed by Bolton et al. can be useful in this assessment.\textsuperscript{42}
In summary, molecular testing for predictive markers may have diagnostic consequences, as they may challenge the initial diagnosis, reveal the presence of a second primary tumor of similar histology or uncover a co-existing disease, the latter of which is especially frequent in hematopoietic diseases. Pathologists and CSMPs need to take these options into account when encountering rare variants, which may require discussion within an MTB.

**Assessing actionability of rare somatic variants in patients with cancer**

A pathogenic somatic mutation can be considered ‘actionable’ when it (potentially) sensitizes a tumor to a specific targeted drug.\(^4^3\) The pathogenicity of a variant is a biological assessment: in cancer, a variant is considered pathogenic when it has been confirmed to induce malignant transformation. However, many somatic variants that have been definitively determined to be pathogenic cannot be considered actionable because no drugs have been developed that effectively target these variants (for example, most \(K\)\(R\)\(A\)\(S\) mutations, which are highly activating but hard to target). Thus, actionability goes beyond the question of pathogenicity and is determined by whether a variant is of predictive relevance in a specific type of cancer. For example, a \(B\)\(R\)\(A\)\(F\) p.(V600E) mutation is actionable with \(B\)\(R\)\(A\)\(F\)/MEK inhibitors in melanoma and NSCLC,\(^4^4,4^5\) but not in colorectal cancer, in which this mutation is only ‘actionable’ with combined \(B\)\(R\)\(A\)\(F\) inhibition and anti-\(E\)\(G\)\(F\)\(R\) therapy.\(^4^6\) Thus, a pathogenic variant cannot unambiguously be classified as ‘actionable’ by itself – rather, actionability is dependent on both cancer type and drug.

**Literature-based assessment of actionability**

In its core, assessment of actionability means identification of published reports that a pathogenic somatic variant confers sensitivity or resistance to a targeted drug in a specific type of cancer. The evidence in these reports can include anything in the range of clinical practice guidelines, meta-analyses, systematic reviews, (randomized) controlled trials, observational or retrospective studies, case studies/reports and *in vivo*, *in vitro* or *in silico* evidence.\(^4^7\) Rare somatic variants are usually too uncommon to be included in anything with a higher level of evidence than observational or retrospective studies, limiting the level of evidence that can be used to support treatment decision-making. In patients discussed in MTBs, the clinical evidence is often limited to case reports or case series. In chapters 2, 7 and 9, it is demonstrated that even limited clinical evidence can result in effective treatment decisions. When clinical evidence is lacking, results from cell viability assays or phosphorylation assays may also be of aid, as demonstrated for \(A\)\(L\)\(K\) resistance mutations in chapter 8. Finally, when there is no clinical or *in vitro* evidence available, a last resort can be results from *in silico* studies or in-house computational molecular modeling.\(^4^8-5^0\) especially
in case of rare variants that may be similar to variants with guidelines-based treatment indications such as \textit{EGFR}, \textit{ALK} and \textit{BRAF}. Molecular modeling will require further clinical validation to determine its optimal role in the routine clinical setting.

Sifting through all the available publications can be too time-consuming to be efficient in routine clinical practice. Therefore, a large variety of resources are available for this purpose (Table 1). Chapter 4 showed that Dutch molecular pathology experts commonly use CKB-JAX,\textsuperscript{51} PubMed,\textsuperscript{52} Google,\textsuperscript{53} My Cancer Genome,\textsuperscript{54} OncoKB,\textsuperscript{55} and CIViC.\textsuperscript{56} It is often useful to consult multiple resources to gather the available evidence, which is facilitated by aggregators such as MetaKB,\textsuperscript{57} and the Molecular Tumor Board Portal (MTBP).\textsuperscript{58} It is recommended that experts preparing cases for MTB meetings consult multiple resources to ensure no relevant available clinical evidence is missed. Examples of such tools are detailed in chapter 4.

### Table 1. Comprehensive tools for interpretation of variant pathogenicity and actionability*

<table>
<thead>
<tr>
<th>Name</th>
<th>Developer</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alissa Interpret</td>
<td>Agilent Technologies, Inc. (Santa Clara, CA)</td>
<td>Commercial</td>
</tr>
<tr>
<td>Cancer Genome Interpreter</td>
<td>Barcelona Biomedical Genomics Lab (IRB Barcelona)</td>
<td>Public</td>
</tr>
<tr>
<td>Clinical Knowledgebase</td>
<td>The Jackson Laboratory</td>
<td>Commercial</td>
</tr>
<tr>
<td>CureMatch Bionov</td>
<td>CureMatch, Inc. (San Diego, CA)</td>
<td>Commercial</td>
</tr>
<tr>
<td>Franklin</td>
<td>Genoox (Palo Alto, CA)</td>
<td>Public</td>
</tr>
<tr>
<td>MH Guide</td>
<td>Molecular Health GmbH (Heidelberg, Germany)</td>
<td>Commercial</td>
</tr>
<tr>
<td>NAVIFY Mutation Profiler</td>
<td>Roche Molecular Systems, Inc. (Santa Clara, CA)</td>
<td>Commercial</td>
</tr>
<tr>
<td>OncoKB</td>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>Public</td>
</tr>
<tr>
<td>QCI Interpret</td>
<td>QIAGEN N.V. (Hilden, Germany)</td>
<td>Commercial</td>
</tr>
<tr>
<td>VarSome</td>
<td>Saphetor SA (Lausanne, Switzerland)</td>
<td>Public</td>
</tr>
</tbody>
</table>

* Only includes commercially or publicly available tools that provide an interpretation of both pathogenicity and actionability. IRB, Institute for Research in Biomedicine; MH, Molecular Health; QCI, QIAGEN Clinical Insight.

### Utility of classification systems to express actionability

Whereas pathogenicity is often classified using the five-tier 2015 ACMG/AMP system, a similarly universally accepted system to classify actionability is lacking. To accommodate the three relevant factors of actionability (variant – cancer type – drug), several classification systems have been proposed. This includes the six-tier 2017 AMP/ASCO/CAP system,\textsuperscript{59} the 11-tier 2018 European Society for Medical Oncology (ESMO)-proposed ‘scale for clinical actionability of molecular targets’ (ESCAT),\textsuperscript{60} and the eight-tier 2019 system proposed by
the German National Center for Tumor Diseases (NCT). Several popular knowledge bases have also developed their own classification system, such as OncoKB, CMC, and CanDL, but these have not been proposed for use in routine diagnostics.

The manner in which these classification systems have been implemented varies. The 2017 AMP/ASCO/CAP system has been adopted by a variety of knowledge bases, such as CKB-JAX, Franklin, MetaKB, and VarSome, whereas the 2018 ESCAT system has only been adopted by the Molecular Tumor Board Portal (MTBP). The 2019 NCT system has been extensively described in publications, but always by the same group of researchers.

These systems all aim to accommodate the three relevant factors for actionability, but this makes them hard to use in routine diagnostics: an inter-rater reliability found a low inter-rater agreement among individual molecular pathology using the 2017 AMP/ASCO/CAP system, relatively the simplest of the three. Chapter 4 demonstrated that the vast majority of CSMPs in the Netherlands currently do not classify variants in terms of actionability. In practice, CSMPs are responsible for gathering evidence regarding potential actionability, and several MTBs in the Netherlands subsequently used the 2017 AMP/ASCO/CAP system to facilitate treatment recommendation in MTB decision-making. One of these included the UMCG-MTB, as reported in chapter 2, which used the system to determine which patients were eligible for discussion within the MTB (Tier 2 variants, as well as combinations between Tier 1, 2 and 3 variants). Furthermore, as demonstrated in chapter 7, the 2017 AMP/ASCO/CAP system was shown to be an effective tool to adequately appreciate evidence regarding the actionability of rare EGFR variants in NSCLC. This chapter demonstrated that grouping ‘rare’ Tier 2, 3 and 4 variants, which is often done in literature, masked the true activity of EGFR-TKI: grouped tier 2 variants (dubbed “uncommon, actionable”) showed similar clinical outcomes as the ‘common’ EGFR p.(L858R). Thus, although using a classification system to grade actionability is beyond the scope of routine diagnostic reporting, these systems – especially the 2017 AMP/ASCO/CAP system – have proven useful to classify actionability within the context of an MTB or in research settings. With the implementation of larger panels and increase in targets predictive of response to therapy, the need to classify actionability to prioritize treatment options will likely increase. Additional studies are required to verify the utility of each system and to investigate which is most applicable in the routine clinical setting.

**Actionability of targeted therapy-induced resistance mechanisms in NSCLC**

Patients with advanced (metastasized) cancer generally have a poor prognosis as opposed to patients with a localized disease stage. This is because, when such patients initiate systemic therapy, progression is inevitable. When faced with an inhibiting agent for a prolonged duration, cancer cells develop novel somatic mutations that bypass the effect of the inhibitor, a phenomenon called ‘oncogene addiction.’ Both on-target (chapter 8)
and off-target (Chapter 9) mechanisms of resistance can be actionable with additional therapies. Resistance mechanisms with evidence of clinical actionability in NSCLC, and testing methods that can be used to detect them, are summarized in Table 2. Routine analysis of resistance mechanisms in these patients can aid both the individual patients as well as enable treatment options for future cancer patients. Clinical trials such as the phase 2 platform trial ORCHARD (NCT03944772), which investigates the actionability of osimertinib-induced resistance mechanisms, are vital in providing high-level evidence for treating these patients. In addition, publishing case reports or case series of patients responding to combination therapy can aid MTBs in providing an optimal treatment recommendation.

<table>
<thead>
<tr>
<th>Alteration</th>
<th>EMA-approved inhibitor</th>
<th>Resistance mechanisms with clinical evidence of actionability</th>
<th>Method to test for resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>MET</strong> amplification(^{74})</td>
<td></td>
</tr>
<tr>
<td><strong>BRAF</strong> p.(V600)</td>
<td></td>
<td>No evidence of clinically actionable resistance mechanisms</td>
<td>RNA analysis</td>
</tr>
<tr>
<td>mutation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EGFR mutation</strong></td>
<td></td>
<td>On-target mutations (G724S, T790M, P794L, C797S(^{49,75-78}))</td>
<td>DNA sequencing</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>MET</strong> amplification(^{79-84})</td>
<td>DNA sequencing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oncogenic kinase fusions (ALK, BRAF, FGFR3, NTRK1, RET, ROS1)(^{85-89})</td>
<td>RNA analysis, IHC (ALK)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>BRAF</strong> V600-mutation (Chapter 9)</td>
<td>DNA sequencing</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>EGFR</strong> amplification (Chapter 2)</td>
<td>DNA sequencing, MLPA</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>ERBB2</strong> amplification and/or HER2 overexpression (Chapter 2)</td>
<td>IHC, DNA sequencing, FISH</td>
</tr>
<tr>
<td><strong>RET fusion</strong></td>
<td>Selpercatinib</td>
<td><strong>MET</strong> amplification(^{80})</td>
<td>DNA sequencing</td>
</tr>
<tr>
<td><strong>ROS1 fusion</strong></td>
<td>Crizotinib Entrectinib</td>
<td>On-target mutations (S1986F, G2032R, D2033N)(^{91-93})</td>
<td>DNA sequencing, FISH</td>
</tr>
</tbody>
</table>

FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; MLPA, multiplex ligation-dependent probe amplification.
Translating actionability to a treatment recommendation within the context of an MTB

When all the available evidence regarding pathogenicity, prevalence and actionability has been gathered, the information can be presented at an MTB meeting, where experts from pathology and oncology prioritize the evidence and regard them in the context of the patient at hand and the availability of targeted drugs. As demonstrated in chapters 2 and 3, Dutch MTBs prioritize guideline-based treatment options, followed by clinical trials and finally, if all of these options have been exhausted, or based on patient preference or performance, an off-label (named patient program or experimental) treatment. Knowing the guidelines-based treatment options, the availability of clinical trials and off-label drugs, and assessing patient performance is the responsibility of attending oncologists. The MTB provides a recommendation to the treating physician.

In summary, the actionability of rare, pathogenic somatic variants and resistance mechanisms should be assessed by CSMPs through an initial literature search, facilitated by online and commercially available tools. The 2017 AMP/ASCO/CAP classification scheme has proven useful to classify actionability within the context of research or when discussing patients in an MTB.

Position of Molecular Tumor Boards within the Dutch healthcare infrastructure

MTBs have been accepted internationally as an indispensable platform for the interpretation of comprehensive molecular diagnostics. To date, methods and/or outcomes of MTBs have been published by over twenty different cancer centers from the United States, United Kingdom, France, Germany, Belgium, and the Netherlands (chapter 2). None of these MTBs are completely similar, as demonstrated in chapter 3 as well as other (international) studies. There have been several attempts to define a common denominator. This includes a report by Luchini et al. comparing the scope and methods of 40 MTBs, and a systematic review by Larson et al. comparing clinical outcomes from 14 MTBs that reported recommendations and subsequent treatment outcomes. In both studies, the proposed scope, organization, composition and position within the healthcare infrastructure of the reported MTBs varied. It is therefore difficult to define an MTB as an entity internationally. The initial raison d’être for most MTBs described in literature is the reciprocal elevation of expertise for oncology experts and molecular pathology experts. Therefore, the closest common definition is that MTBs are a type of multidisciplinary team (MDT) meeting in which experts from oncology and molecular pathology discuss the clinical interpretation of molecular results. Only recently, discussion of specific cases within the context of an MTB has become recommended by guidelines or required as a condition for reimbursement of subsequent diagnostics or therapy. The Dutch National Health Care Institute has recently recommended MTBs as a central platform for interpreting molecular
diagnostic results, which has been discussed in Dutch Parliament. Therefore, it is vital that the scope and organization of an MTB as well as its position within the healthcare infrastructure is defined nationally. In addition, quality assessment guidelines are necessary.

**Scope and organization of MTBs and the ‘Dutch MTB model’**

A comparison of Dutch MTBs has been performed thrice. Van der Velden *et al.* and Willemsen *et al.* assessed differences between a selection of Dutch MTBs. Chapter 3 expanded on this evidence by comparing all eight Dutch tertiary cancer referral center-associated MTBs in 2019. This study demonstrated that, despite organizational differences, there were similarities that could be used to define a common denominator, and a subsequent comparison between treatment recommendations demonstrated 86% agreement in identifying actionable targets. The common denominator was dubbed the ‘Dutch MTB model’ and represents a national ‘best practice’ consensus on the minimal requirements for the implementation of a tertiary cancer referral center-associated MTB. It encompasses seven conditions, presented in chapter 3, with regards to the composition, scope, connection to conventional cancer type-specific MDTs and peripheral hospital, the types of recommendations, reporting of recommendations and evaluation of adherence and outcome.

In terms of composition, a Dutch MTB features at least (thoracic, medical, hematological, and/or pediatric) oncologists, molecular-oriented pathologists, and CSMPs. These three experts attended every tertiary cancer referral center-associated MTB in the Netherlands. Clinical geneticists and bioinformaticians can be valuable contributors when discussing results with germline implications and large-scale sequencing results (such as WGS), respectively. The Dutch Society for Lung Diseases and Tuberculosis (NVALT) has recommended this composition for MTBs that discuss NSCLC patients. The UMCG-MTB also featured structural biologists and clinical researchers. MTBs published in literature reported a variety of other types of attendees, including radiation or surgical oncologists, radiologists, trial coordinators, pharmacists, nurses, social workers, and patient advocates. MTBs that include surgeons, radiation oncologists and radiologists, such as those at the University of Alabama at Birmingham and the San Diego Moores Cancer Center, are effectively ‘enhanced’ conventional MDTs.

In terms of scope, an MTB operating in a tertiary cancer referral center in the Netherlands is the multidisciplinary platform for clinical interpretation of rare molecular diagnostic results in oncology, with a reciprocal educative purpose for experts from oncology and molecular pathology. Beyond this, the scope of an MTB is dependent on two factors: the eligible cancer type(s) and the complexity of results discussed. For cancer types, there are two types of MTBs: cancer type-agnostic and cancer type-specific MTBs. Most MTBs described
in literature are cancer type-specific,\textsuperscript{94,95} with a few exceptions: MTBs at the Centre George-François Leclerc in Dijon (lung cancer) and the Columbia University Medical Center in New York (hematological cancer) were cancer type-specific.\textsuperscript{101,111} In the Netherlands, most MTBs were cancer type-agnostic, but two MTBs were NSCLC-specific, because most (predictive) molecular diagnostics were performed for this cancer type (chapter 3). One of these reviewed all molecular results, resulting in an average of 15 cases per meeting, whereas the UMCG-MTB (the subject of chapter 2), open for any type of cancer but limited to rare or complex results, discussed an average of 3.8 cases per weekly meeting. Cancer centers maintaining a cancer type-specific MTB would have to establish additional cancer type-specific MTBs to accommodate other oncological subspecialties with patients requiring interpretation of molecular results. Alternatively, representatives from these subspecialties can attend cancer type-agnostic or -specific MTBs at other cancer centers. The second factor, the complexity of results, is more difficult to categorize, as a result that is hard to interpret today may be standard-of-care when new evidence becomes available. Therefore, although subspecialties may recommend review of specific rare results by an MTB (as the NVALT requires for specific NSCLC cases),\textsuperscript{121} it is not meaningful to restrict which patients are eligible for MTB review in central guidelines. Rather, it is up to each cancer center to determine which structure (cancer type-specific versus cancer type-agnostic and all molecular results vs only complex results) best fits their volume, demand and time.

**Kinship between (academic) MTBs and conventional, cancer type-specific MDTs or peripheral hospitals**

There are major differences between MTBs and conventional, cancer type-specific MDTs. The Dutch comprehensive cancer organization (IKNL) defines a conventional MDT as a “cancer type-specific discussion of patients, in which patients are presented and recommendations are formulated regarding the desired treatment, diagnostics and care, based on regional and national guidelines and tailored to the individual patient.”\textsuperscript{122} MDTs are thus organized for each oncological subspecialty and integrate clinical information, imaging, laboratory results and pathological assessment to determine the patient’s stage of disease and the subsequent guidelines-based (‘standard-of-care’) choice of treatment. Oncology guidelines often require that treatment decisions be made in consultation with a conventional MDT.\textsuperscript{121} MTBs operating according to the Dutch MTB model are complementary to existing MDTs, and it can happen that patients are discussed in both a conventional MDT and an MTB. However, as demonstrated by chapter 3 and in literature, MTBs often review only a selection of (difficult) cases to allow time for an elaborate biological and clinical discussion, rationalizing treatment options beyond guidelines,\textsuperscript{95} whereas conventional MDTs are fast-paced and review large volumes of patients at the directive of current guidelines.\textsuperscript{122} Thus, MTBs can serve as a platform for those cases that are too complex in terms of molecular
results to be briefly reviewed by a conventional MDT. To ensure MTB recommendations do not interfere with those provided by conventional MDTs, arrangements should be made that allow a connection between the two. To facilitate this, MTBs should feature oncologists and pathologists who also participate in conventional MDTs. Participation of MTB-associated CSMPs in conventional MDTs could further enhance this interaction. It should the responsibility of an MTB to ensure these interactions are established.

The Dutch MTB model presented in chapter 3 states that MTBs should be associated with tertiary cancer referral centers, but should be open for participation by physicians, pathologists and CSMPs from peripheral hospitals and pathology laboratories. This does not mean convey that meetings regarding molecular diagnostic testing results should not be held in peripheral hospitals, as a reciprocal elevation of expertise is also valuable in peripheral hospitals and may not be achieved in the fast-paced conventional MDT meetings. However, such ‘molecular meetings’ should not adversely impact individual patients’ access to therapeutic options. Physicians in peripheral hospitals in the Netherlands diagnose and treat large volumes of patients, whereas oncologists at tertiary cancer referral centers usually treat the more complex cases. The tertiary oncologists are often more experienced at treating patients beyond guidelines, as they host clinical trials or have experience treating patients off-label (in compassionate use). Therefore, guaranteeing individual patients’ access to available therapeutic options is only possible through collaboration between peripheral hospitals and referral centers, which can be established in both ways. First, representatives from peripheral hospitals could submit cases to central MTB meetings at tertiary cancer referral centers and participate in the discussions through videoconferencing to learn to recognize difficult cases and discuss their own patients. In addition, experts from tertiary cancer referral centers can join ‘molecular meetings’ at peripheral hospitals to provide guidance on treatment options available at the tertiary center. It is in patients’ best interest that (molecular) experts representing MTBs at tertiary cancer referral centers implement both interactions to ensure a close collaboration with pathologists and treating physicians from peripheral hospitals in regional ‘MTB federations’.

**The MTB recommendation and beyond**

MTB recommendations can be diagnostic or therapeutic. Diagnostic recommendations cover any appropriate molecular diagnostic test to identify potential targets and therapeutic recommendations generally differentiate between targeted therapeutic options (be it in standard-of-care, within a clinical trial or off-label). The MTB can also differentiate between non-targeted treatment modalities such as chemotherapy and immunotherapy when this choice depends on molecular diagnostic results: for example, some molecular markers (TMB, MMRd or a T cell-inflamed gene expression profile) are histology-agnostic markers for response to immunotherapy. To ensure a recommendation reaches a patient’s treating
physician, a report needs to be formulated and entered into the patient’s electronic health record in accordance with the quality criteria established by the IKNL’s guideline for MDT reporting.\textsuperscript{122}

As MTB recommendations often transcend guideline-based treatments, evaluation of adherence and outcome of MTB recommendations is pivotal. To this end, the UMCG-MTB maintained a local registry of reviewed cases with a systematic follow-up to evaluate outcome (\textit{chapter 2}). A systematic follow-up and registry of adherence and outcome reinforces the educative nature of MTBs and allows clinical researchers to evaluate patterns of response in cohorts of patients with rare actionable variants. In effect, MTB recommendations can benefit both the individual patient as well as future generations of cancer patients.

In summary, the MTB has become an essential tool in the interpretation of challenging molecular testing results. Tertiary cancer referral center-associated MTBs in the Netherlands should adhere to the ‘Dutch MTB model’. Establishment of cancer type-specific or peripheral ‘molecular meetings’ (complementary to conventional MDTs) is valuable, but interaction with tertiary cancer referral center-associated MTBs in regional ‘MTB federations’ is necessary to ensure patients have equal chances to receive the most optimal targeted treatment options.

**FUTURE PERSPECTIVES**

Molecular diagnostic tests have been solidified as indispensable tools in pathology and oncology. Indications for performing molecular profiling are continuously expanding and the comprehensiveness of multi-gene panel tests are improving. In effect, the volume of patients receiving molecular diagnostic testing as well as the complexity of results will increase. This section highlights several challenges that are likely to result from these developments.

**Expanding access to targeted therapy and risk of ‘target fever’**

There are yet gains to be made in ensuring patients eligible for targeted therapy are tested for the presence of a predictive molecular marker. In \textit{chapter 7}, it was demonstrated that in 2017 (when \textit{EGFR} testing had been standard-of-care for several years), 19.1% of eligible patients were still not tested for the presence of \textit{EGFR} mutations. Another Dutch study found that 11% of eligible patients with gastrointestinal stromal tumors (GIST) were not tested for relevant predictive markers in 2017–2018.\textsuperscript{126} Beyond guidelines-based treatment, patients with advanced cancer may also be eligible for treatment with targeted drugs in clinical trials or off-label (named patient programs) when standard-of-care treatment options are
exhausted. For example, the Dutch adaptive precision-oncology Drug Rediscovery Protocol (DRUP) allows treatment of NSCLC patients in case of ERBB4 mutations (afatinib) or MAP2K1/NRAS mutations (trametinib), but these markers are currently not recommended by NVALT, and patients are thus not routinely tested for these markers in most laboratories. In addition, targeted therapies are available in clinical trials for patients whose cancers are not routinely tested for molecular markers at initial diagnosis. As a consequence, their access to treatment options at this stage is affected by inter-laboratory variation in gene panels used to profile tumors or the possibility to profile a tumor within trials.

One option to harmonize access to targeted treatment options is to reimburse (extensive) predictive molecular profiling in routine diagnostics for patients who have exhausted standard treatment options. The downside of such an approach for other patients is that a surplus of patients would be tested for actionable targets whereas the likelihood of detecting an actionable variant is negligible. This can lead to ‘target fever’: treating physicians may irrationally hope to offer their patients targeted therapy despite the earlier detection of a mutually exclusive driver, or they may inadvertently consider a reported variant of unknown significance (VUS) as actionable and treat the patient with an ineffective drug. To avoid ‘target fever’, and to increase the cost-effectiveness of this approach, patients should be evaluated within an MTB for eligibility based on factors such as performance status, the odds of finding an actionable target (taking into account the co-existence of other driver alterations) and the availability of corresponding targeted drugs prior to requesting molecular profiling. A similar approach is already used for specific indications in several Dutch MTBs (as demonstrated in chapter 3), and is standard procedure for patients discussed in MTBs at the Institut Curie in Paris and the University of Alabama at Birmingham Hospital. If all patients who have exhausted treatment options but have not undergone molecular diagnostic testing will indeed be offered broad-panel profiling, reviewing eligibility of these patients in a central MTB will significantly increase its burden. This will instigate the establishment of ‘spin-off’ MTBs for this purpose.

**Prospect of routine implementation of whole-genome sequencing**

The routine use of WGS for cancer patients has been investigated in the Netherlands in several large clinical trials, such as the DRUP and the ‘WGS Implementation in standard Diagnostics for Every cancer patient’ (WIDE) trial. These trials demonstrated a high concordance between WGS and standard-of-care diagnostics for detecting small-scale variants (~98%) and copy-number alterations (CNA) such as amplifications (97%) and deletions (100%), whereas the concordance with gene fusions was lower (91.3%). Currently, studies disagree whether WGS is a cost-effective alternative to routine diagnostics. Some
experts nevertheless advocate offering every patient with advanced or metastatic cancer WGS at least once during the course of their disease.\textsuperscript{133} However, this approach has several disadvantages and challenges that would need to be addressed.

First, not all actionable targets can be reliably detected using WGS: for fusion genes, the concordance between WGS and standard-of-care diagnostics was 91.3%.\textsuperscript{129} This may be due to the complexity of detecting fusions in DNA: fusions can involve multiple break junctions in intronic regions.\textsuperscript{129} As a result, a significant proportion of patients with (potentially) actionable fusions would not receive matched therapy when tested with WGS. In addition, false-positives may also be detected with WGS, as a DNA fusion that is in-frame and is predicted to lead to a viable fusion gene may in practice not lead to expression of a pathogenic fusion transcript. In both cases, it would be necessary to test patients with an RNA-based test in addition to WGS.

Second, it is unlikely that WGS will completely replace panel-based molecular tests, for several reasons. WGS is currently mostly of interest for unrestricted actionable target analysis, but for diagnostic indications, single-gene tests or small panels could suffice. In addition, current WGS methods require a fresh-frozen sample with sufficient tumor content and high yields of DNA.\textsuperscript{129} Not only is this not always (anatomically or clinically) possible to acquire, but for patients with recurrent disease who were previously been treated with curative intent, molecular tests are often performed on archival tissue. Furthermore, peripheral hospitals often outsource molecular diagnostics to other centers, whereas they do not routinely perform fresh frozen biopsies. For these indications, different single-gene and multi-gene tests will likely continue to be necessary.

Third, performing WGS for large volumes of patients will significantly increase the complexity of bioinformatics pipelines and interpretation of results for molecular pathology experts. For patients with CUP, for whom WGS is now reimbursed, the Dutch health authorities require discussion of WGS results within the context of an MTB before initiating targeted therapy,\textsuperscript{117} and it may also be necessary to discuss these patients in a ‘pre-WGS MTB’ to evaluates whether they are indeed eligible for WGS. Annually, around 1300 patients are diagnosed with CUP in the Netherlands.\textsuperscript{14} If all of these patients were tested with WGS, it would come down to an increase in volume of approximately 4-5 patients/MTB/week (for each of eight MTBs), which is around the amount MTBs in the Netherlands already discuss on a weekly basis (\textbf{chapter 3}). Thus, if the reimbursement for WGS is expanded to other types of cancer, the burden of current MTBs will surely outweigh their capacity. Offering WGS to every patient may then require the establishment of ‘spin-off’ MTBs, for example cancer type-specific MTBs. Interaction with a more centrally organized MTB would be preferential, as was discussed in the previous paragraph.
In summary, WGS is a promising tool that will likely be increasingly used in standard-of-care molecular diagnostics. Offering WGS to every patient with advanced or metastatic cancer would harmonize patients’ chances of receiving optimal therapy. If WGS is offered in routine cancer diagnostics, several issues need to be addressed, such as the increased complexity of results. Current MTBs have insufficient capacity to accommodate all these results and the infrastructure of MTBs would therefore need to be expanded. If WGS is indeed integrated into routine diagnostics, the need for large-panel sequencing will likely remain.

**Towards inter-institutional molecular data sharing**

As a result of the expansion of the available molecular testing panels and targeted drugs, MTBs frequently discuss molecular profiles that have not been described before or for which the therapeutic consequences are unclear. In effect, each MTB represents a unique cohort of patients with rare molecular profiles and treatment outcomes, effectively a large collection of unpublished case reports. To ensure this information is not lost, the UMCG-MTB (chapter 2) structurally evaluates and registers adherence and subsequent treatment outcomes after MTB recommendations. This can be of benefit to future patients with similar profiles, especially when it concerns response to experimental or off-label drugs. In addition, this serves to educate attending pathology and oncology experts and as an internal quality assessment of MTB performance. These treatment outcomes would not be structurally registered otherwise. To enhance this effect of MTBs, and to allow patients across the nation an equal chance to receive a potentially successful drug, the Predictive Analysis for Therapy (PATH) project established a shared database among tertiary cancer referral center-associated MTBs.\[^{135}\] The first version of this database (cBioPortal-MTB) was established in October 2019, using the web-based cBioPortal resource as a backbone and hosted by the Dutch Translational Research IT (TraIT) infrastructure.\[^{136}\] As of October 2021, four MTBs were sharing a total of 432 unique cases, and access had been provided to representatives of two other MTBs. The effectiveness of this molecular data sharing initiative is limited by several challenges which will need to be tackled in the near future.

The first challenge is that precautions need to be taken to ensure the privacy of patients is protected in according with the European Union’s General Data Protection Regulation 2016/679 (GDPR) and the Dutch Medical Treatment Contracts Act (WGBO).\[^{137,138}\] These regulations state that inter-institutional sharing of patient and tumor characteristics is only possible when the information is anonymized, unless patients have provided informed consent. However, it is difficult to set up a unified and integrated informed consent system for every patient who is reviewed by a Dutch MTB. As a solution, the cBioPortal-MTB only contains information relating to the type of cancer and the molecular profiles that were
detected, without identifiable patient codes. This limits the utility of this database because treatment recommendation, decision and subsequent outcomes are not readily available, but needs to be manually retrieved for each data request.

A second issue is that MTBs require a local infrastructure that facilitates the input and extraction of cases that they have reviewed. In addition, for proper treatment decision-making, the actual status of response needs to be continuously revised for patients previously discussed in an MTB. However, most MTBs do not have such systems, or if they do, with limited options to extract (anonymized) data. MTBs that want to participate need to ensure that there are such systems before they can share their data. The MTBs will need to be motivated to invest in such a structure without directly apperceiving an advantage, as a dataset of rare cases will require at least several months or years of input before they contain enough cases to be of use for others. As a result, after two years, half of the tertiary cancer referral center-associated MTBs were still not sharing cases in this database.

These challenges are yet to be solved. One solution that is currently being explored is to integrate the database into the PALGA network. The utility of this network for the purpose of molecular data-sharing is dependent on whether representatives from MTBs would be able to search in other institutions’ data, whether a distinction can be made between cases discussed by MTBs or not and whether linkage with treatment outcome is possible. Furthermore, as the Netherlands is a relatively small country, reaching out to MTBs in other countries to provided data in cBioPortal-MTB would increase the utility of the database.

In summary, each MTB represents a unique collection of patients with rare somatic variants corresponding treatment outcomes. This information is valuable for future patients with similar alterations and should therefore be shared among institutions. The cBioPortal-MTB database, which was established for this purpose, requires expansion in terms of volume and information to become a useful tool for MTBs around the country and beyond.

**CONCLUSIONS**

The clinical utility of molecular diagnostic tests is continuously increasing. Tumor mutational profiling is therefore becoming more extensive, and rare molecular results are encountered more often. This poses a challenge for diagnostic and therapeutical decision-making in the interpretation of molecular results for oncologists, pathologists and CSMPs. The findings in this thesis highlighted these challenges and provided strategies to cope with them. In routine diagnostics, CSMPs are primarily responsibility for the classification of pathogenicity and interpretation of potential actionability in preparation of MTB meetings.
This responsibility is supported by a variety of online resources that facilitate access to \textit{in vitro} and clinical evidence. In more complex cases, a core tool that is indispensable in institutions offering broad-panel molecular profiling techniques is the Molecular Tumor Board. The ‘Dutch MTB model’ encompasses a consensus of the minimal requirements for an MTB associated with a tertiary cancer referral center in the Netherlands. Adherence to these requirements and inter-institutional collaborations between MTBs as well as regional ‘MTB federations’ involving central MTBs, conventional cancer type-specific multidisciplinary teams and peripheral experts are essential to ensure patients across the nation have equal access to targeted therapeutic treatment options.
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