INESSS
LE SAVOIR PREND FORME

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ÉTAT DES CONNAISSANCES

Profilage moléculaire des tumeurs solides adultes

Focus Panel[MC] (Illumina[MC]) – Analyse de 52 biomarqueurs somatiques

Annexes complémentaires

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

Direction de l'évaluation des médicaments et des technologies à des fins de remboursement

Québec

Le présent document contient les annexes complémentaires au rapport intitulé *Profilage moléculaire des tumeurs solides adultes. Focus Panel^{MC} (Illumina^{MC}) – Analyse de 52 biomarqueurs somatiques*. Le contenu de cette publication a été rédigé et édité par l'INESSS.

Ces annexes et le rapport final sont accessibles en ligne dans la section *Publications* de notre site *Web*.

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Responsabilité

L'Institut rend accessibles les principales informations qui ont servi à la préparation du rapport *Profilage moléculaire des tumeurs solides adultes. Focus Panel^{MC} (Illumina^{MC}) – Analyse de 52 biomarqueurs somatiques* aux lecteurs qui désirent plus de détails sur sa démarche scientifique.

Ce document n'a pas fait l'objet d'une révision linguistique. Il ne reflète pas forcément les opinions des autres personnes consultées aux fins du présent dossier.

TABLE DES MATIÈRES

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ANNEXE A

Méthodologie

La démarche d'évaluation comprend une revue rapide structurée de la documentation scientifique et grise pour le volet clinique et économique, une analyse d'impact budgétaire, ainsi que des consultations auprès d'experts locaux. Les positions et constats de l'INESSS qui sont rapportés sont basés sur l'ensemble des données scientifiques extraites, des positions et lignes directrices émises par les principales sociétés savantes consultées, ainsi que sur les données contextuelles et les savoirs expérientiels recueillies.

Questions d'évaluation

1) Est-il cliniquement pertinent d'utiliser un panel multigénique et une approche par séquençage de nouvelle génération (SNG) comme l'AmpliSeq^{MC} Focus Panel (Illumina^{MC}) pour le diagnostic, le pronostic et l'identification de cibles thérapeutiques des tumeurs solides?

2) Est-ce que l'approche par panel multigénique selon une méthode de SNG pour effectuer l'analyse des tumeurs solides est efficiente?

3) Quel serait l'impact budgétaire potentiellement associé à l'implantation de ce type d'analyses?

4) Quels sont les enjeux cliniques, économiques et organisationnels potentiellement associés à l'utilisation clinique de ce panel multigénique effectué par SNG?

Stratégies de repérage de l'information scientifique et de la littérature grise

Les stratégies de recherche, qui incluent des mots-clés du vocabulaire libre et contrôlé (MeSH), ont été élaborées en collaboration avec un conseiller en information scientifique de l'INESSS (Annexe B). Les documents publiés en français ou en anglais à partir de 2010 ont été considérés.

Les bases de données suivantes ont été interrogées : MEDLINE, Embase et EBM Reviews (Cochrane Database of Systematic Reviews, Health Technology Assessment et NHS Economic Evaluation Database).

La recherche d'information a été complétée par la consultation de sites Web de sociétés savantes, d'organisations professionnelles, réglementaires et gouvernementales d'intérêt (Annexe C). Une recherche manuelle des références des publications jugées pertinentes a également été effectuée.

Sélection des publications, extraction et synthèse des données publiées

Les devis d'études considérés étaient les rapports d'évaluation des technologies et des modes d'intervention en santé, les guides de pratique clinique et les revues systématiques avec ou sans méta-analyse. Les études ont été sélectionnées par le professionnel scientifique responsable de l'évaluation en fonction des critères PIPOH suivants :

- Population à qui s'adresse l'intervention : Patients atteints d'un cancer solide ciblé par le demandeur (cancer du poumon, cancer colorectal, tumeurs stromales gastro-intestinales, mélanome, cancer de la thyroïde, cancer de la vessie/ carcinome urothélial);
- Intervention : Analyse par SNG de l'ADN somatique de tumeurs solides;
- Professionnels à qui s'adressent les travaux : Pathologistes moléculaires, oncologues et autres professionnels impliqués dans la prise en charge des patients atteints d'une tumeur solide, gestionnaires de réseaux de santé, instance gouvernementale et règlementaire en santé et service sociaux;
- Résultat d'intérêt [de l'anglais *Outcome*] : Recommandations et lignes directrices en lien avec l'utilisation du SNG pour l'analyse des tissus somatiques, l'implantation en contexte clinique et le remboursement de l'analyse;
- Milieu de soins [de l'anglais *Health care setting*] : Milieux cliniques spécialisés en oncologie, préférentiellement (sans s'y restreindre) dans des juridictions comparables au Québec, notamment avec un système public de soins et services de santé.

Le diagramme de sélection des publications est présenté à l'annexe D. Les données d'intérêt extraites sont présentées à l'annexe F. Les principaux constats sont résumés dans le rapport sous forme d'une synthèse narrative supportée par des tableaux au besoin.

Évaluation de la qualité méthodologique des publications sélectionnées

L'évaluation de la qualité méthodologique des publications sélectionnées a été effectuée par le professionnel scientifique responsable du rapport à l'aide de l'outil AGREE GRS (*Appraisal of Guidelines for Research and Evaluation – Global Rating Scale Instrument*). Les publications étaient jugées de bonne qualité méthodologique avec un score global fixé arbitrairement à 75 % ou plus; de qualité modérée avec un score global de 50 % à 74 %; de faible qualité avec un score global de 25 % à 49 %; et de très faible qualité avec un score global de moins de 25 %. Les résultats de cette évaluation sont présentés à l'annexe E.

Collecte et synthèse des données contextuelles et expérientielles

Des experts ont été consultés afin de recueillir l'information pertinente à l'évaluation. Le recrutement a été effectué en collaboration avec les ordres et associations professionnels concernés de façon à représenter les différentes spécialités médicales et milieux de pratique engagés dans la prise en charge des patients concernées. Les données contextuelles et les savoirs expérientiels recueillis auprès des experts sont

résumés sous forme de synthèse narrative en exposant les principaux constats dans la section *Considérations d'implantations* (section 7).

Validation et assurance qualité

Une validation du document a été effectuée par la coordination scientifique et la direction responsable de sa production. Une validation du gabarit utilisé et de la transparence des aspects méthodologiques a été réalisée en collaboration avec la Vice-présidence scientifique de l'INESSS par le Bureau – Méthodologie et éthique. Une validation finale du rapport a été effectuée par la Vice-présidence scientifique de l'INESSS. Le document n'a pas fait l'objet d'une lecture externe.

Prévention, déclaration et gestion des conflits d'intérêts et de rôles

Toutes les personnes qui ont collaboré à ces travaux ont déclaré les intérêts personnels qui pouvaient les placer dans une situation propice au développement de conflits d'intérêts, qu'ils soient commerciaux, financiers, relatifs à la carrière, relationnels ou autres. Elles ont également déclaré les différentes activités professionnelles ou les rôles qui pouvaient les placer dans une situation propice au développement de conflits de rôles. Une telle déclaration a été faite sur la base du formulaire standardisé applicable à l'INESSS. Les déclarations remplies ont fait l'objet d'une évaluation par l'INESSS, laquelle a permis de déterminer les modalités de gestion à appliquer selon les situations déclarées. Le cas échéant, les conflits d'intérêts et de rôles déclarés sont divulgués dans les pages liminaires du rapport.

ANNEXE B

Stratégie de recherche documentaire

MEDLINE (Ovid) **Date du repérage : février 2022** **Limites : 2010- ; anglais, français**	
1	exp High-Throughput Nucleotide Sequencing/
2	(deep sequencing* OR ((high-throughput OR high-through-put) ADJ (nucleotide sequence* OR nucleotide sequencing* OR rna sequencing* OR sequence analys* OR sequencing*)) OR ((illumina OR ion proton OR ion torrent) ADJ sequencing*) OR massive parallel sequencing* OR massively-parallel sequencing* OR mps OR next-gen sequence* OR next-gen sequencing* OR next-generation sequence* OR next-generation sequencing* OR ngs).ti,ab
3	(((gene* OR multigene OR multi-gene) ADJ panel*) OR panel test*).ti,ab
4	1 OR 2 OR 3
5	(((biochemical OR biologic* OR clinical OR immun* OR laboratory OR serum) ADJ marker*) OR biomarker*).ti
6	(surrogate ADJ (endpoint* OR end point* OR marker*)).ti
7	(prognos* ADJ marker*).ti
8	((((individuali#ed OR personali#ed OR precision OR predictive) AND (medicine OR oncology)) OR p-health).ti
9	(target* ADJ2 therap*).ti
10	(diagnos* OR screen* OR test OR testing OR tests).ti
11	(5 OR 6 OR 7 OR 8 OR 9) AND 10
12	*Colorectal Neoplasms/di,ge
13	(colorectal ADJ3 (cancer* OR carcinoma* OR neoplasm* OR tumor* OR tumour*)).ti
14	12 OR 13
15	*Melanoma/di,ge
16	melanom*.ti,ab
17	15 OR 16
18	(solid ADJ3 (neoplasm* OR tumor* OR tumour*)).ti,ab
19	14 OR 17 OR 18
20	(4 OR 11) AND 19
21	*Biomarkers, Tumor/an,ge
22	exp *Genetic Testing/ OR *Molecular Diagnostic Techniques/ OR exp *Sequence Analysis, DNA/
23	((sequence* OR sequencing*) ADJ3 (dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna)).ti
24	((sequence* OR sequencing*) ADJ3 (analys* OR evaluation* OR technique* OR technolog*)).ti
25	((dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna) ADJ3 (analys* OR data* OR diagnos* OR evaluation* OR expression profil* OR screen* OR technique* OR technolog* OR test OR testing OR tests)).ti
26	(21 OR 22 OR 23 OR 24 OR 25) AND 19
27	exp Guideline/ OR exp Guidelines as Topic/ OR Health Planning Guidelines/ OR exp Consensus/ OR exp Consensus Development Conference/ OR exp Critical Pathways/ OR Clinical Conference.pt OR exp Clinical Protocols/ OR (guideline* OR guide line* OR CPG OR CPGs OR guidance OR practical guide* OR consensus OR (clinical ADJ2 (path OR paths OR pathway* OR protocol*)) OR ((critical OR clinical) ADJ2 (path OR paths OR pathway*)) OR committee opinion* OR position statement* OR practice parameter* OR practice pathway* OR practice protocol* OR recommendation*).ti,ab,kw OR (position* OR statement*).ti
28	Meta-Analysis.pt OR Systematic Review/ OR exp Technology Assessment,Biomedical/ OR (meta-analy* OR metaanaly* OR met analy* OR metanaly* OR meta-review* OR metareview* OR meta regression* OR metaregression* OR meta synthesis OR metasynthesis OR overview of review* OR overviews of reviews OR (systematic* ADJ3 (review* OR overview* OR literature OR search* OR research*)) OR ((quantitative OR methodologic* OR integrativ*) ADJ (review* OR overview* OR synthes*)) OR umbrella review* OR HTA OR HTAs OR technology assessment* OR technology overview* OR technology appraisal* OR technology reassessment*).ti,ab,kw
29	exp Guideline/ OR (guideline* OR guideline* OR CPG OR CPGs OR guidance OR practical guide*).ti
30	20 AND (27 OR 28)
31	26 AND 29
32	30 OR 31
33	(Case Reports OR Comment OR Editorial OR Letter).pt OR (case report* OR comment* OR reply OR replies OR editorial* OR letter*).ti
34	32 NOT 33
35	Animals/ NOT (Humans/ AND Animals/)
36	34 NOT 35

Embase (Ovid) Date du repérage : février 2022 Limites : 2010- ; anglais, français	
1	exp High Throughput Sequencing/
2	(deep sequencing* OR ((high-throughput OR high-through-put) ADJ (nucleotide sequence* OR nucleotide sequencing* OR rna sequencing* OR sequence analys* OR sequencing*)) OR ((illumina OR ion proton OR ion torrent) ADJ sequencing*) OR massive parallel sequencing* OR massively-parallel sequencing* OR mps OR next-gen sequence* OR next-gen sequencing* OR next-generation sequence* OR next-generation sequencing* OR ngs).ti,ab
3	(((gene* OR multigene OR multi-gene) ADJ panel*) OR panel test*).ti,ab
4	1 OR 2 OR 3
5	(((biochemical OR biologic* OR clinical OR immun* OR laboratory OR serum) ADJ marker*) OR biomarker*).ti
6	(surrogate ADJ (endpoint* OR end point* OR marker*)).ti
7	(prognos* ADJ marker*).ti
8	((((individuali#ed OR personali#ed OR precision OR predictive) AND (medicine OR oncology)) OR p-health).ti
9	(target* ADJ2 therap*).ti
10	(diagnos* OR screen* OR test OR testing OR tests).ti
11	(5 OR 6 OR 7 OR 8 OR 9) AND 10
12	*Colorectal Tumor/di
13	(colorectal ADJ3 (cancer* OR carcinoma* OR neoplasm* OR tumor* OR tumour*)).ti
14	12 OR 13
15	*Melanoma/di
16	melanom*.ti,ab
17	15 OR 16
18	*Solid Malignant Neoplasm/di
19	(solid ADJ3 (neoplasm* OR tumor* OR tumour*)).ti,ab
20	18 OR 19
21	14 OR 17 OR 20
22	(4 OR 11) AND 21
23	*DNA sequencing/ OR *Gene Sequence/ OR *Genetic Screening/ OR *Molecular Diagnosis/
24	((sequence* OR sequencing*) ADJ3 (dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna)).ti
25	((sequence* OR sequencing*) ADJ3 (analys* OR evaluation* OR technique* OR technolog*)).ti
26	((dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna) ADJ3 (analys* OR data* OR diagnos* OR evaluation* OR expression profil* OR screen* OR technique* OR technolog* OR test OR testing OR tests)).ti
27	(23 OR 24 OR 25 OR 26) AND 21
28	Clinical Pathway/ OR Clinical Protocol/ OR Consensus/ OR Consensus Development/ OR Health Care Planning/ OR exp Practice Guideline/ OR (guideline* OR guide line* OR CPG OR CPGs OR guidance OR practical guide* OR consensus OR (clinical ADJ2 (path OR paths OR pathway* OR protocol*)) OR ((critical OR clinical) ADJ2 (path OR paths OR pathway*)) OR committee opinion* OR position statement* OR practice parameter* OR practice pathway* OR practice protocol* OR recommendation*).ti,ab,kw OR (position* OR statement*).ti
29	Biomedical Technology Assessment/ OR Meta Analysis/ OR Systematic Review/ OR (meta-analy* OR metaanaly* OR met analy* OR metanaly* OR meta-review* OR metareview* OR meta regression* OR metaregression* OR meta synthesis OR metasynthesis OR overview of review* OR overviews of reviews OR (systematic* ADJ3 (review* OR overview* OR literature OR search* OR research*)) OR ((quantitative OR methodologic* OR integrativ*) ADJ (review* OR overview* OR synthes*)) OR umbrella review* OR HTA OR HTAs OR technology assessment* OR technology overview* OR technology appraisal* OR technology reassessment*).ti,ab,kw
30	exp Practice Guideline/ OR (guideline* OR guideline* OR CPG OR CPGs OR guidance OR practical guide*).ti
31	22 AND (28 OR 29)
32	27 AND 30
33	31 OR 32
34	Case Report/ OR Editorial/ OR Letter/ OR (case report* OR comment* OR reply OR replies OR editorial* OR letter*).ti
35	33 NOT 34
36	Conference Abstract.pt
37	35 NOT 36
38	Nonhuman/ NOT (Human/ AND Nonhuman/)
39	37 NOT 38

EBM Reviews (Ovid) : Cochrane Database of Systematic Reviews; Health Technology Assessment; NHS Economic Evaluation Database **Date du repérage : février 2022** **Limites : 2010- ; anglais, français**	
1	(deep sequencing* OR ((high-throughput OR high-through-put) ADJ (nucleotide sequence* OR nucleotide sequencing* OR rna sequencing* OR sequence analys* OR sequencing*)) OR ((illumina OR ion proton OR ion torrent) ADJ sequencing*) OR massive parallel sequencing* OR massively-parallel sequencing* OR mps OR next-gen sequence* OR next-gen sequencing* OR next-generation sequence* OR next-generation sequencing* OR ngs).ti,ab
2	(((gene* OR multigene OR multi-gene) ADJ panel*) OR panel test*).ti,ab
3	1 OR 2
4	(((biochemical OR biologic* OR clinical OR immun* OR laboratory OR serum) ADJ marker*) OR biomarker*).ti,ab
5	(surrogate ADJ (endpoint* OR end point* OR marker*)).ti,ab
6	(prognos* ADJ marker*).ti,ab
7	(((individuali#ed OR personali#ed OR precision OR predictive) AND (medicine OR oncology)) OR p-health).ti,ab
8	(target* ADJ2 therap*).ti,ab
9	(diagnos* OR screen* OR test OR testing OR tests).ti,ab
10	(4 OR 5 OR 6 OR 7 OR 8) AND 9
11	3 OR 10
12	(colorectal ADJ3 (cancer* OR carcinoma* OR neoplasm* OR tumor* OR tumour*)).ti,ab
13	melanom*.ti,ab
14	(solid ADJ3 (neoplasm* OR tumor* OR tumour*)).ti,ab
15	12 OR 13 OR 14
16	11 AND 15

ANNEXE C

Recherche de la littérature grise

SITES WEB / ORGANISATIONS ET DE SOCIÉTÉS SAVANTES CONSULTÉES	PUBLICATIONS RETENUES, N
Évaluation des technologies de santé – Guides de pratique	
INESSS (Institut national d'excellence en santé et en services sociaux) www.inesss.qc.ca	3
ACMTS/CADTH (Agence canadienne des médicaments et des technologies de la santé/ Canadian Agency for Drugs and Technologies in Health) www.cadth.ca	0
HAS (Haute Autorité de Santé, France) www.has-sante.fr	0
NICE (National Institute for Health and Care Excellence) www.nice.org.uk	0
EUnetHTA (European Network for Health Technology Assessment) www.eunethta.eu	0
INAHTA (International Network of Agencies for Health Technology Assessment-Alberta) www.inahta.org	0
HTAi (Health Technology Assessment International-Alberta) www.htai.org	0
G-I-N (Guidelines International Network) www.g-i-n.net	0
SIGN (Scottish Intercollegiate Guidelines Network) www.sign.ac.uk	0
AHRQ (Agency for Healthcare Research and Quality) www.ahrq.gov	0
NHS (National Health Service) www.nhs.uk/pages/home.aspx	0
HQO (Health Quality Ontario) www.hqontario.ca	0
OHTAC (Ontario Health Technology Advisory Committee) www.hqontario.ca	0
AHS (Alberta Health Services) www.albertahealthservices.ca	0
HTA Unit (Health Technology Assessment Unit - University of Calgary) http://vortal.htai.org	0
Cancer Council Australia https://wiki.cancer.org.au/australia/Guidelines	1
German Guideline Program in Oncology (GGPO) https://www.leitlinienprogramm-onkologie.de/english-language/	1
Épidémiologie - Statistiques sur la santé	
Statistique Canada www.statcan.gc.ca	0
Banque de données RAMQ (Régie de l'assurance maladie du Québec)	0
Société canadienne du cancer https://cancer.ca/fr/	1
Hématologie – Oncologie	
NCCN (National Comprehensive Cancer Network) www.nccn.org	6
ESMO (European Society for Medical Oncology) www.esmo.org	8
ASCO (American Society of Clinical Oncology) www.asco.org	2
Pathologie	
CAP (College of American Pathologists) www.cap.org	3
AMP (Association for Molecular Pathology) www.amp.org	2
ASCP (American Society for Clinical Pathology) https://www.ascp.org/	0
TOTAL	**27**

ANNEXE D

Diagramme de flux de la sélection des publications du volet clinique

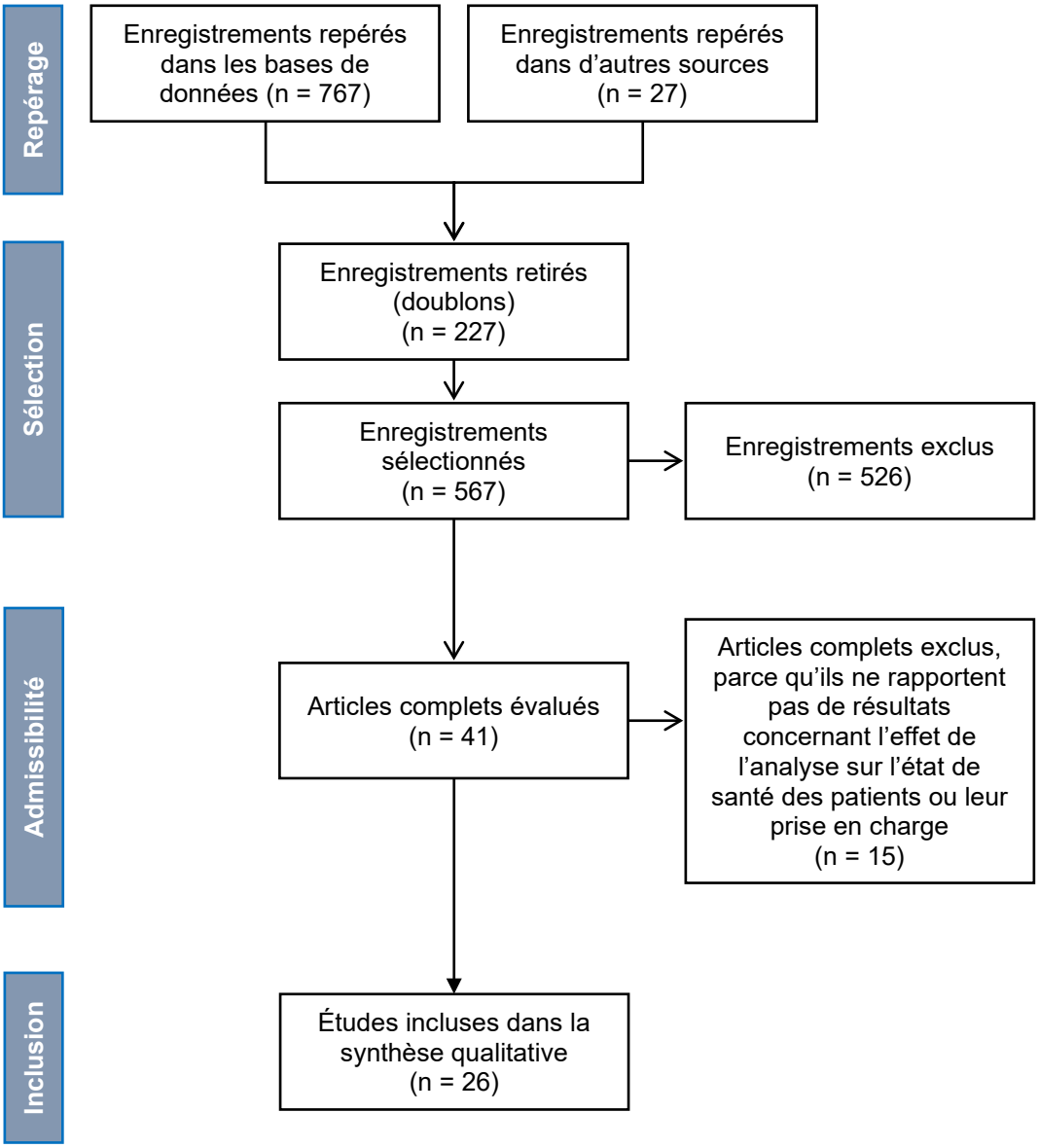
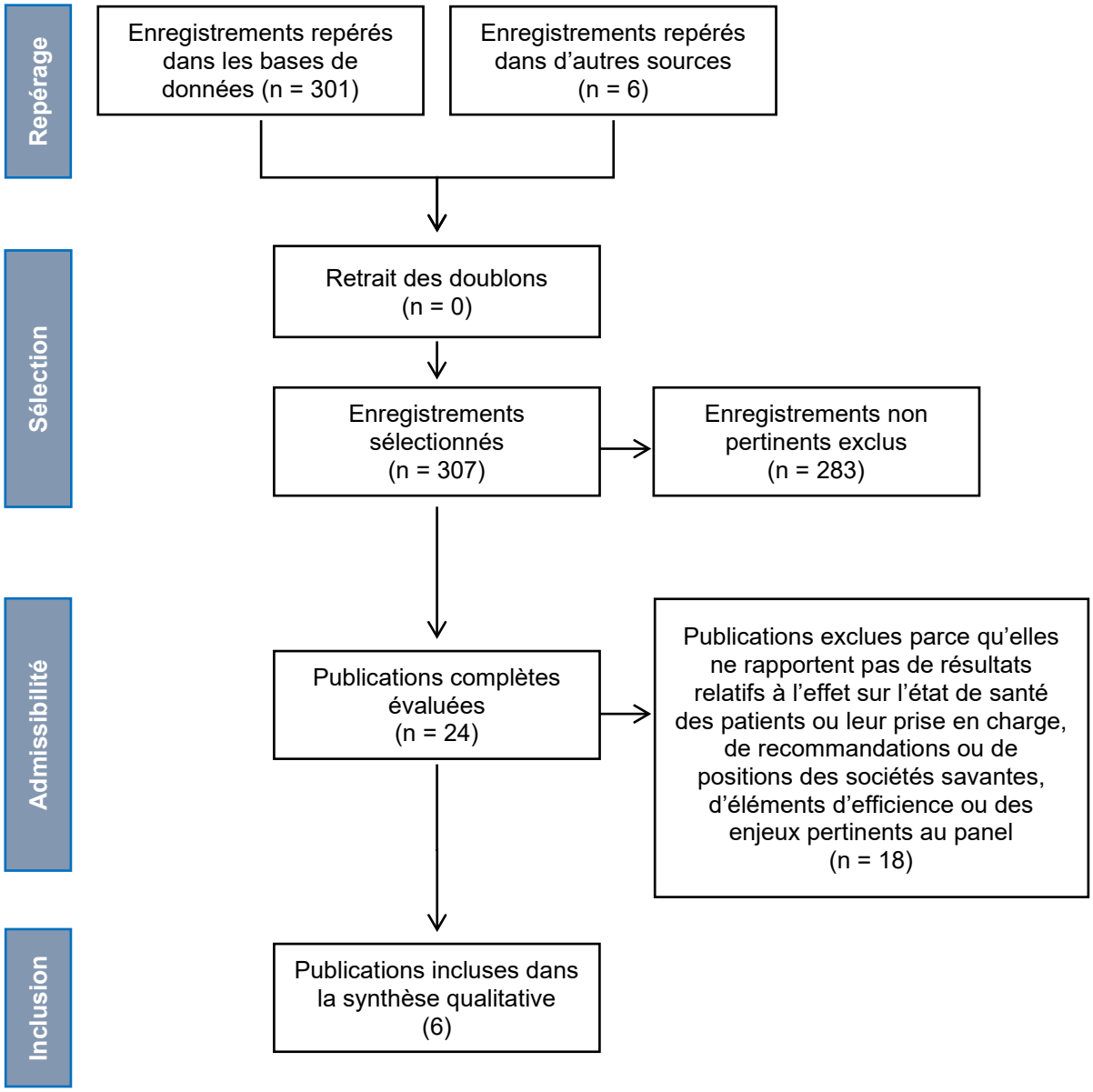


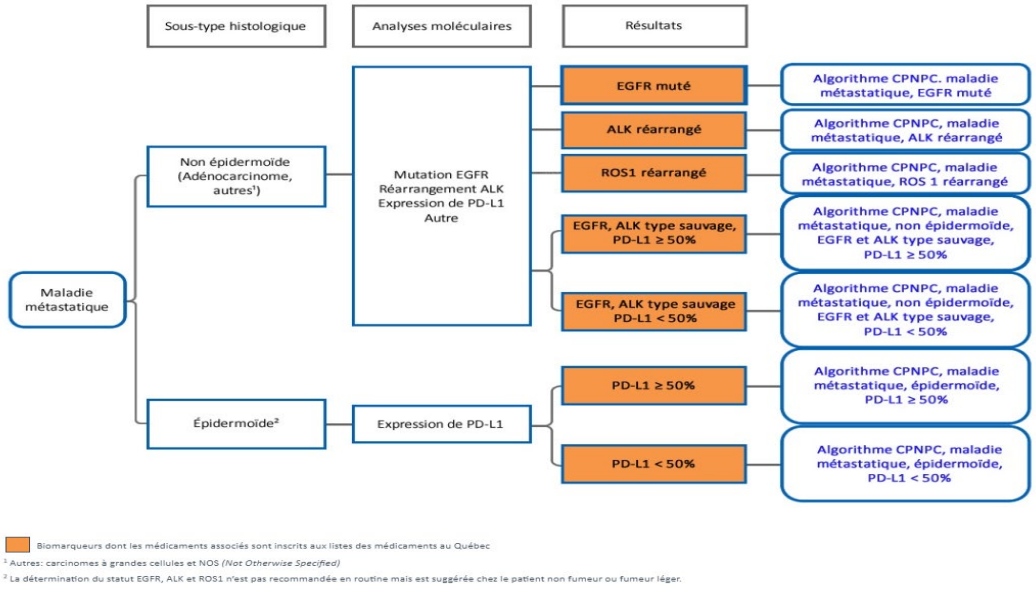
Diagramme de flux de la sélection des publications du volet économique



ANNEXE E

Données extraites des documents sélectionnés

Tableau E-1 Données extraites des documents publiés par des agences règlementaires, autorités de santé et sociétés savantes – volet clinique

ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
Cancer du poumon non à petites cellules	
Institut national d'excellence en santé et en services sociaux (INESSS) et Groupe d'étude en oncologie du Québec (GÉOQ). [INESSS et GÉOQ, 2022]	***Algorithmes d'investigation, de traitement et de suivi du cancer du poumon*** 1.8 CPNPC métastatique, avancé ou inopérable 

ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
ESMO [Mosele *et al.*, 2020]	***Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: A report from the ESMO Precision Medicine Working Group*** (2020 Aug 24) **Table 2. Summary recommendations**

Tumour types	General recommendations for daily practice	Recommendation for clinical research centres	Special considerations for patients
Lung adenocarcinoma	Tumour multigene NGS to assess level I alterations. Larger panels can be used on the basis of specific agreements with pay taking into account the overall cost of the strategy (drug included[a]) and if they repo accurate ranking of alterations. NGS can be done on RNA or DNA, if it includes level I fusions in the panel.	It is highly recommended that clinical research centres perform multigene sequencing in the context of molecular screening programmes in order to increase access to innovative drugs and to speed up clinical research. This is particularly relevant in breast, pancreatic and hepatocellular cancers where level IIeIV alterations are numerous.	Using large panels of genes could lead to few clinically meaningful responders, not detected by small panels or standard testings. In this context and outside the diseases where large panels of genes are recommended, ESMO acknowledges that a patient and a doctor could decide together to order a large panel of genes, pending no extra cost for the public health care system, and if the patient is informed about the low likelihood of benefit.
Squamous cell lung cancers	No current indication for tumour multigene NGS		
Breast cancers	No current indication for tumour multigene NGS		
Colon cancers	Multigene tumour NGS can be an alternative option to PCR if it does not result in additional cost.		
Prostate cancers	Multigene tumour NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy and if they report accurate ranking of alterations.		
Gastric cancers	No current indication for tumour multigene NGS		
Pancreatic cancers	No current indication for tumour multigene NGS		
Hepatocellular carcinoma	No current indication for tumour multigene NGS		
Cholangiocarcinoma	Multigene tumour NGS could be recommended to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug includeda) and if they report accurate ranking of alterations. RNA-based NGS can be used.		
Others	Tumour multigene NGS can be used in ovarian cancers to determine somatic BRCA1/2 mutations. In this latter case, larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug includeda) and if they report accurate ranking of alterations. Large panel NGS can be used in carcinoma of unknown primary.		

ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
	<table><tr><td></td><td>It is recommended to determine TMB in cervical cancer, salivary cancer, thyroid cancers, well-to-moderately differentiated neuroendocrine tumours, vulvar cancer, pending drug access (and in TMB-high endometrial and SCL cancers if anti-PD1 antibody is not available otherwise).</td><td></td><td></td></tr></table> anti-PD1, anti-programmed cell death 1; DRUP, drug rediscovery protocol; ESMO, European Society for Medical Oncology; NGS, next-generation sequencing; SCL, small-cell lung cancer; TMB, tumour mutational burden. [a] ESMO recommends using off-label drugs matched to genomics only if an access programme and a procedure of decision have been developed at the national or regional level, as illustrated by the DRUP programme.
College of American Pathologists, International Association for the Study of Lung Cancer, Association for Molecular Pathology [Lindeman *et al.*, 2018]	***Updated Molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: Guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology*** (2018 Jan 22) Strong Recommendation 1. ROS1 testing must be performed on all lung advanced stage adenocarcinoma patients, irrespective of clinical characteristics. Expert consensus opinion 2. ROS1 IHC may be used as a screening test in lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method. 3. BRAF molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include BRAF as part of larger testing panels performed either initially or when routine EGFR, ALK, and ROS1 testing are negative. 4. RET molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include RET as part of larger testing panels performed either initially or when routine EGFR, ALK, and ROS1 testing are negative. 5. ERBB2 (HER2) molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include ERBB2 (HER2) mutation analysis as part of a larger testing panel performed either initially or when routine EGFR, ALK, and ROS1 testing are negative. 6. KRAS molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include KRAS as part of larger testing panels performed either initially or when routine EGFR, ALK, and ROS1 testing are negative. 7. MET molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include MET as part of larger testing panels performed either initially or when routine EGFR, ALK, and ROS1 testing are negative. Recommendation 8. IHC is an equivalent alternative to FISH for ALK testing. Emerging Markers for Molecular Testing in Lung Cancer ▪ Mitogen-activated protein kinase kinase 1 (MEK1/MAP2K1) ▪ Fibroblast growth factor receptor 1-4 (FGFR 1-4) ▪ Neurotrophic tyrosine kinase, receptor, type 1-3 (NTRK1-3) ▪ Neuregulin 1 (NRG1) ▪ Ras-like without CAAX 1 (RIT1) ▪ Neurofibromin 1 (NF1) ▪ Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit ▪ alpha (PIK3CA)

ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
	▪ AKT serine/threonine kinase 1 (AKT1) ▪ NRAS proto-oncogene, GTPase (NRAS) ▪ Mechanistic target of rapamycin (MTOR) ▪ Tuberous sclerosis 1 (TSC1) ▪ Tuberous sclerosis 2 (TSC2) ▪ KIT proto-oncogene receptor tyrosine kinase (KIT) ▪ Platelet-derived growth factor receptor alpha (PDGFRA) ▪ Discoidin domain receptor tyrosine kinase 2 (DDR2)
American Society of Clinical Oncology [Kalemkerian *et al.*, 2018]	***Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update*** (2018 Feb 05) 1. Recommendation: ROS1 testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics. 2. Expert Consensus Opinion: ROS1 IHC may be used as a screening test in patients with advanced lung adenocarcinoma; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method. 3. Expert Consensus Opinion: BRAF testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics. 4. Expert Consensus Opinion: RETmolecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include RETas part of larger testing panels performed either initially or when routine EGFR, ALK, BRAF, and ROS1 testing is negative. 5. Expert Consensus Opinion: ERBB2 (HER2) molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include ERBB2 (HER2) mutation analysis as part of a larger testing panel performed either initially or when routine EGFR, ALK, BRAF, and ROS1 testing is negative. 6. Expert Consensus Opinion: KRAS molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include KRAS as part of larger testing panels performed either initially or when routine EGFR, ALK, BRAF, and ROS1 testing is negative. 7. Expert Consensus Opinion: MET molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include METas part of larger testing panels performed either initially or when routine EGFR, ALK, BRAF, and ROS1 testing is negative. 8. Recommendation: IHC is an equivalent alternative to FISH for ALK testing.
ESMO [Planchard *et al.*, 2020]	***Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*** (15 september 2020) <u>Recommendations – Pathology/Molecular biology</u> • *EGFR* mutation status should be systematically analysed in advanced NSCC [I, A]. Test methodology should have adequate coverage of mutations in exons 18–21, including those associated with resistance to some therapies [III, B]. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 *L858R* point mutation) should be determined [I, A] • Testing for *ALK* rearrangement should be systematically carried out in advanced non-squamous NSCLC [I, A] • Detection of the *ALK* translocation by FISH remains a standard, but IHC with high-performance ALK antibodies and validated assays may be used for screening [III, A] and have recently been accepted as an equivalent alternative to FISH for ALK testing • Testing for *ROS1* rearrangement should be systematically carried out in advanced NSCLC [III, A]. Detection of the *ROS1* translocation by

<table>
<tr><th>ORGANISATIONS,
[AUTEUR, ANNÉE]
HYPERLIEN</th><th>TITRE DU DOCUMENT (DATE DE PUBLICATION)
RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT</th></tr>
<tr><td></td><td>FISH remains a standard; IHC may be used as a screening approach [IV, A]
• BRAF V600 mutation status should be systematically analysed in advanced NSCLC for the prescription of BRAF/MEK inhibitors [II, A]
• Testing for NTRK rearrangement should be systematically carried out in advanced NSCLC [III, A]. Screening for NTRK rearrangements may use IHC or NGS, with appropriate testing follow-up to validate a positive result [IV, A]
• Molecular EGFR and ALK testing are not recommended in patients with a confident diagnosis of SCC, except in unusual cases, e.g. never/former light smokers or long-time ex-smokers [IV, A]
• If available, multiplex platforms (NGS) for molecular testing are preferable [III, A]. Whatever testing modality is used, it is mandatory that adequate internal validation and quality control measures are in place and that laboratories participate in, and perform adequately in, external quality assurance schemes for each biomarker test [III, A].</td></tr>
<tr><td>Chinese Society of Clinical Oncology (CSCO), European Society for Medical Oncology (ESMO)

[Wu et al., 2019]</td><td>Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: A CSCO–ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS (2019 Feb)

2d. EGFR mutation status should be systematically analysed in advanced NSCC [A=100% and I, A]. Test methodology should have adequate coverage of mutations in exons 18–21, including those associated with resistance to some therapies [A=100% and III, B]. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 L858R point mutation) should be determined [A=100% and I, A].
2e. Testing for ALK rearrangement should be systematically carried out in advanced NSCC [A=100% and I, A].
2f. Detection of the ALK translocation by FISH remains a standard, but IHC with high-performance ALK antibodies and validated assays may be used for screening [A=100% and III, A] and have recently been accepted as an equivalent alternative to FISH for ALK testing.
2g. Testing for ROS1 rearrangement should be systematically carried out in advanced NSCC [A=100% and II, A]. Detection of the ROS1 translocation by FISH remains a standard. A validated RT-PCR test may be used as an alternative. IHC may be used as a screening approach [A=100% and IV, A].
2h. BRAF V600 mutation status should be systematically analysed in advanced NSCC for the prescription of BRAF/MEK inhibitors [A=100% and II, A].
2i. Molecular EGFR and ALK testing is not recommended in patients with a confident diagnosis of SCC, except in unusual cases, e.g. never/former light smokers or long-time ex-smoker [A¼100% and IV, A].
2j. If available, multiplex platforms for molecular testing are preferable [A=100% and III, A].</td></tr>
<tr><td>NCCN – NSCLC

[NCCN, 2022a]</td><td>Non-Small Cell Lung Cancer – Version 3.2022 (March 16, 2022)

Adenocarcinoma, Large cell, NSCLC not otherwise specified (NOS), molecular testing, including:
▪ EGFR mutation (category 1), ALK (category 1), KRAS, ROS1, BRAF, NTRK1/2/3, METex14 skipping, RET
▪ Testing should be conducted as part of broad molecular profiling

Squamous cell carcinoma, consider molecular testing, including:
▪ EGFR mutation, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, METex14 skipping, RET
▪ Testing should be conducted as part of broad molecular profiling

<u>Emerging biomarkers to identify novel therapies for patients with metastatic NSCLC</u>
<table>
<tr><th>Genetic Alteration (ie, Driver event)</th><th>Available Targeted Agents with Activity Against Driver Event in Lung Cancer</th></tr>
<tr><td>High-level MET amplification</td><td>Crizotinib, Capmatinib</td></tr>
<tr><td>ERBB2 (HER2) mutations</td><td>Ado-trastuzumab emtansine, Fam-trastuzumab deruxtecan-nxki</td></tr>
</table></td></tr>
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ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
	KRAS (KRAS proto-oncogene) point mutations: KRAS is a G-protein with intrinsic GTPase activity, and activating mutations result in unregulated signaling through the MAP/ERK pathway. ▪ Mutations in KRAS are most commonly seen at codon 12, although other mutations can be seen in NSCLC. ▪ The presence of a KRAS mutation is prognostic of poor survival when compared to patients with tumors without KRAS mutation. ▪ Mutations in KRAS have been associated with reduced responsiveness to EGFR TKI therapy. Targeted therapy or immunotherapy for advanced or metastatic disease ***EGFR* Mutation Positive** (eg, *exon 19* deletion or *L858R*) • First-line therapy ▸ Afatinib[1] ▸ Erlotinib[2] ▸ Dacomitinib[3] ▸ Gefitinib[4,5] ▸ Osimertinib[6] ▸ Erlotinib + ramucirumab[7] ▸ Erlotinib + bevacizumab* (nonsquamous)[8] • Subsequent therapy ▸ Osimertinib[9] ***EGFR exon 20* insertion mutation positive** • Subsequent therapy ▸ Amivantamab-vmjw[10] ***KRAS G12C* mutation positive** • Subsequent therapy ▸ Sotorasib[11] ***ALK* Rearrangement Positive** • First-line therapy ▸ Alectinib[12,13] ▸ Brigatinib[14] ▸ Ceritinib[15] ▸ Crizotinib[12,16] ▸ Lorlatinib[17] • Subsequent therapy ▸ Alectinib[18,19] ▸ Brigatinib[20] ▸ Ceritinib[21] ▸ Lorlatinib[22] ***ROS1* Rearrangement Positive** • First-line therapy ▸ Ceritinib[23] ▸ Crizotinib[24] ▸ Entrectinib[25] • Subsequent therapy ▸ Lorlatinib[26] ▸ Entrectinib[25] ***BRAF* V600E Mutation Positive** • First-line therapy ▸ Dabrafenib/trametinib[27] • Subsequent therapy ▸ Dabrafenib/trametinib[28,29] ***NTRK1/2/3* Gene Fusion Positive** • First-line/Subsequent therapy ▸ Larotrectinib[30] ▸ Entrectinib[31] ***MET* Exon 14 Skipping Mutation** • First-line therapy/Subsequent therapy ▸ Capmatinib[32] ▸ Crizotinib[33] ▸ Tepotinib[34] ***RET* Rearrangement Positive** • First-line therapy/Subsequent therapy ▸ Selpercatinib[35] ▸ Pralsetinib[36] ▸ Cabozantinib[37,38] ▸ Vandetanib[39] **PD-L1 ≥1%** • First-line therapy** ▸ Pembrolizumab[40-42] ▸ (Carboplatin or cisplatin)/pemetrexed/ pembrolizumab (nonsquamous)[43] ▸ Carboplatin/paclitaxel/bevacizumab*/ atezolizumab (nonsquamous)[44] ▸ Carboplatin/(paclitaxel or albumin-bound paclitaxel)/pembrolizumab (squamous)[45] ▸ Carboplatin/albumin-bound paclitaxel/ atezolizumab (nonsquamous)[46] ▸ Nivolumab/ipilimumab[47] ▸ Nivolumab/ipilimumab/pemetrexed/ (carboplatin or cisplatin) (nonsquamous)[48] ▸ Nivolumab/ipilimumab/paclitaxel/carboplatin (squamous)[48] **PD-L1 ≥50% (in addition to above)** • First-line therapy** ▸ Atezolizumab[49] ▸ Cemiplimab-rwlc[50]
Cancer colorectal	
INESSS et GÉOQ [INESSS et GÉOQ, 2016a; INESSS et GÉOQ, 2016b]	***Algorithmes d'investigation, de traitement et de suivi – cancer du rectum*** (Mai 2016) ***Algorithmes d'investigation, de traitement et de suivi – cancer du côlon*** (Mai 2016) 2.2 Pathologie ▪ La recherche de mutations pour le gène RAS (KRAS et NRAS) doit être faite chez tous les patients ayant un cancer colorectal chez qui un traitement avec un anti-EGFR est considéré. Une analyse du statut de RAS devrait minimalement inclure les codons 12, 13, 61, 117 et 146 du gène KRAS et les codons 12, 13, 59 et 61 de NRAS. ▪ L'analyse de la mutation du gène BRAF, en conjonction avec l'analyse de l'instabilité des microsatellites ou non, apporte une information additionnelle sur le pronostic, mais elle n'ajoute pour l'instant aucun élément supplémentaire à propos du choix d'un traitement pour le patient.

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ASCP, CAP, AMP, ASCO [Sepulveda *et al.*, 2017]	***Molecular biomarkers for the evaluation of colorectal cancer: Guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology*** (June 15, 2021) Strength of Recommendation: Recommendation 1. Patients with colorectal carcinoma being considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include KRAS and NRAS codons 12 and 13 of exon 2, 59 and 61 of exon 3, and 117 and 146 of exon 4 ("expanded" or "extended" RAS). 2a. BRAF p.V600 (BRAF c.1799 [p.V600]) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal carcinoma for prognostic stratification. 2b. BRAF p.V600 mutational analysis should be performed in deficient MMR tumors with loss of MLH1 to evaluate for Lynch syndrome risk. Presence of a BRAF mutation strongly favors a sporadic pathogenesis. The absence of a BRAF mutation does not exclude risk of Lynch syndrome. 3. Clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification. Strength of Recommendation: No Recommendation 4. There is insufficient evidence to recommend BRAF c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors. 5. There is insufficient evidence to recommend PIK3CA mutational analysis of colorectal carcinoma tissue for therapy selection outside of a clinical trial. Note: Retrospective studies have suggested improved survival with postoperative aspirin use in patients whose colorectal carcinoma harbors a PIK3CA mutation. 6. There is insufficient evidence to recommend PTEN analysis (expression by immunohistochemistry or deletion by fluorescence in situ hybridization) in colorectal carcinoma tissue for patients who are being considered for therapy selection outside of a clinical trial.
Van Cutsem *et al.*, 2016	***ESMO consensus guidelines for the management of patients with metastatic colorectal cancer*** (July 2016) Recommendation 4: *RAS* testing • *RAS* mutational status is a negative predictive biomarker for therapeutic choices involving EGFR antibody therapies in the metastatic disease setting [I, A] • *RAS* testing should be carried out on all patients at the time of diagnosis of mCRC [I, A] • *RAS* testing is mandatory before treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab [I, A] • A network of arrangements should be established to ensure the rapid and robust transit of tissue samples from referral centres to testing laboratories, to minimise the turnaround time and avoid delays in having this information available for all patients with mCRC • *RAS* analysis should include at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117) • Turnaround time for *RAS* testing (expanded *RAS* analysis) should be ≤7 working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens. Recommendation 5: *BRAF* testing • Tumour *BRAF* mutation status should be assessed alongside the assessment of tumour RAS mutational status for prognostic assessment (and/or potential selection for clinical trials) [I, B]

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	Recommendation 8: Emerging biomarkers not recommended for routine patient management outside of a clinical trial setting: • Detection of mutations in *PIK3CA* exon 20 [II, D] • Evaluation of PTEN loss by IHC [V, D] • Evaluation of the levels of the EGFR ligands amphiregulin, epiregulin and transforming growth factor-α [II, D] • Evaluation of levels of *EGFR* protein expression [II, E] • Evaluation of *EGFR* amplification and copy number and EGFR ectodomain mutations [IV, D] • Evaluation of *HER2* amplification or *HER2* activating mutations • Evaluation of *HER3*, and *MET* receptor overexpression [IV, D]
ESMO-JSMO [Yoshino *et al.*, 2018]	***Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: A JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS*** (2018 Jan) Recommendation 4 with revision: RAS testing 4a. RAS mutational status is a predictive biomarker for therapeutic choices involving EGFR antibody therapies in the metastatic disease setting [I, A]. ▪ RAS testing should be carried out on all patients at the time of diagnosis of mCRC [I, A] 4b. RAS testing is mandatory before treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab [I, A]. Recommendation 5 with revision: BRAF testing 5. Tumour BRAF mutation status (V600E) should be assessed alongside the assessment of tumour RAS mutational status for prognostic assessment [I, B]. Recommendation 8: emerging biomarkers 8a. Detection of mutations in PIK3CA, exon 20 is optional [II, D].
NCCN – Colon cancer [NCCN, 2022b]	***Colon Cancer – Version 1.2022*** (February 25, 2022) KRAS, NRAS, and BRAF Mutation Testing ▪ All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) and BRAF mutations individually or as part of an NGS panel. Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab. BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor.
CAP [Bartley *et al.*, 2014]	***Template for reporting results of biomarker testing of specimens from patients with carcinoma of the colon and rectum*** (2013 Jun 28) D: PIK3CA Mutational Analysis. PIK3CA mutations activate the PI3K-PTEN-AKT pathway that is downstream from both the EGFR and the RAS-RAF-MAPK pathways. PIK3CA mutation and subsequent activation of the AKT pathway have been shown to play an important role in colorectal carcinogenesis and have been associated with KRAS mutation12 and microsatellite instability.13 PIK3CA mutation has further been associated with poor survival in resectable stage I to III colon cancer, with the adverse effect of PIK3CA mutation potentially limited to patients with KRAS wild-type tumors.14 PIK3CA mutations have been associated with resistance to anti-EGFR therapy in several studies,15,16 but not in others.17 The reasons for the discrepancy are not clear. Mutations of exons 1, 9, and 20 of the PIK3CA gene represent .95% of known mutations.

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	A European consortium recently suggested that only PIK3CA exon 20 mutations are associated with a lack of cetuximab activity in KRAS wild-type tumors and with a shorter median progression-free survival and overall survival. 16 By contrast, exon 9 PIK3CA mutations are associated with KRAS mutations and do not have an independent effect on cetuximab efficacy.16 More studies are needed to establish the prognostic and predictive roles of PIK3CA exon-9 and exon-20 mutations.
Cancer Council of Australia [Cancer Council Australia, 2017]	***Clinical practice guidelines for the prevention, early detection and management of colorectal cancer*** (2018 January) <u>Optimal molecular profiling of colorectal cancer</u> *RAS* mutation studies should be performed on patients with advanced (metastatic) colorectal cancer in whom anti-EGFR treatment is being considered. Cetuximab and panitumumab should only be considered for the treatment of patients with *RAS* wild-type metastatic colorectal cancer. (Grade D) There is emerging evidence suggesting that *BRAF* mutation may be associated with poor response to anti-EGFR treatment, and that *BRAF* mutation studies should therefore be performed on patients with advanced (metastatic) colorectal cancer. (Grade D) <u>Molecular pathology and biomarkers – implications for systemic therapy</u> ▪ RAS testing should be carried out on all patients at the time of diagnosis of metastatic colorectal cancer. ▪ RAS mutational status is a negative predictive biomarker for therapeutic choices involving EGFR antibody therapies in metastatic colorectal cancer. ▪ The BRAF mutation status should ideally be performed at the time of diagnosis of metastatic colorectal cancer, as this represents a distinct biologic subtype. ▪ The presence of a BRAF mutation in metastatic colorectal cancer is considered a poor prognostic marker. ▪ The preponderance of the available evidence is that response to EGFR-targeted agents is less likely in patients whose tumours harbour a BRAF mutation.
German Guideline Program in Oncology (GGPO) [GGPO, 2019]	***Evidenced-based Guideline for Colorectal Cancer*** (January 2019) <u>9.2 Initial Molecular Biological Diagnostics Prior to Commencing Therapy</u> If possible, (All) RAS and BRAF mutations shall be determined prior to initiating first-line therapy. (Grade A, LoE 1a) <u>9.8 Selection of Systemic Therapy Depending on the Molecular Pathological Subgroup and the Tumour Localisation</u> Patients found to have a RAS wild type (RAS-wt) in an extended RAS analysis (KRAS and NRAS, exons 2-4) and with a left-sided primary tumour (colon cancer) shall preferably be treated with doublet chemotherapy plus anti-EGFR therapy in the first-line therapy of the metastatic disease. (Grade A, LoE 1a) Doublet chemotherapy should be used primarily in patients with a RAS mutation. Whether triplet therapy is better than doublet therapy or whether bevacizumab should be used has not been confirmed. (Grade B, LoE 3a) Patients with a BRAF mutation should primarily receive the most effective chemotherapy, e.g. triplet therapy, or be enrolled in a clinical study. (Grade B, LoE 4)

ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
Tumeur stromal gastro-intestinale	
NCCN – Gastrointestinal Stromal Tumors [NCCN, 2021b]	***Gastrointestinal Stromal Tumors (GISTs) – Version 1.2021*** (October 30 2021) <u>PRINCIPLES OF MUTATION TESTING</u> ▪ Approximately 80% of GISTs have a mutation in the gene encoding the KIT receptor tyrosine kinase; another 5%–10% of GISTs have a mutation in the gene encoding the related PDGFRA receptor tyrosine kinase. The presence and type of KIT and PDGFRA mutations are not strongly correlated with prognosis. ▪ The mutations in KIT and PDGFRA in GISTs result in expression of mutant proteins with constitutive tyrosine kinase activity. Testing for KIT and PDGFRA mutations should be performed if TKIs are considered as part of the treatment plan since the presence of mutations (or absence of mutations) in specific regions of the KIT and PDGFRA genes are correlated with response (or lack of response) to specific TKIs. ▪ Specific mutations in KIT or PDGFRA show some correlation with tumor phenotype, but mutations are not strongly correlated with the biologic potential of individual tumors. The accumulated data show that KIT mutations are not preferentially present in high-grade tumors, and can also be found in small incidental tumors as well as tumors that have an indolent course. Similary, mutational analysis of PDGFRA cannot be used to predict the behavior of individual tumors. ▪ GISTs have different response rates to imatinib based upon the tumor mutation status: 90% for tumors that have KIT exon 11 mutation, and 50% for tumors that have a KIT exon 9 mutation; the likelihood of response improves with the use of imatinib 400 mg BID. Most PDGFRA mutations are associated with a response to imatinib, with the exception of D842V, which is unlikely to respond to imatinib and most other approved TKIs for GIST except avapritinib. ▪ Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in KIT or PDGFRA. Sunitinib treatment is indicated for patients with imatinib-resistant tumors or imatinib intolerance. Regorafenib is indicated for patients with disease progression on imatinib and sunitinib. Referral to clinical trial is strongly recommended for patients with mutations resistant to imatinib, sunitinib, regorafenib, ripretinib, and avapritinib. ▪ About 10%–15% of GISTs lack mutations in KIT or PDGFRA. The vast majority of these GISTs have functional inactivation of the succinate dehydrogenase (SDH) complex, which can be detected by lack of expression of SDHB on IHC. Inactivation of the SDH complex may result from a mutation or from epigenetic silencing. A small minority of GISTs that retain SDH expression have alternative driver mutations. ▪ Testing for alternative driver mutations is indicated for tumors that are negative for KIT or PDGFRA mutations. Testing includes assessment for SDHB deficiency by IHC for gastric tumors and SDH mutation testing for SDHB-deficient tumors by IHC. in addition, next-generation sequencing (NGS) testing for alternative driver mutations (eg, BRAF, NF1, NTRK, and FGFR fusions) should be performed for potential identification of a targeted therapy.
ESMO-EURACAN [Casali *et al.*, 2022]	***Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up*** (2018 Oct) <u>MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE – Recommendations</u> ▪ In the case of KIT exon 9 mutation, adjuvant imatinib at a higher dose of 800 mg daily for 3 years may be considered [II, B; ESCAT score: I-A]. ▪ PDGFRA exon 18 D842V-mutated GISTs should not be treated with adjuvant therapy [IV, D]. ▪ If R0 surgery is not feasible or implies major sequelae and the tumour harbours a sensitive mutation, preoperative treatment with imatinib is standard [III, A]. In case of PDGFRA-D842V mutation, neoadjuvant avapritinib may be considered [III, A: ESMO-MCBS v1.1 score: 3; ESCAT score: I-B].

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MANAGEMENT OF ADVANCED/METASTATIC DISEASE – Recommendations

- Imatinib is the standard first-line treatment for locally-advanced, inoperable and metastatic patients, except for GIST without KIT/PDGFRA mutations or with a PDGFRA exon 18 D842V mutation [I, A]. The standard dose of imatinib is 400 mg daily [I, A].
- Standard first-line treatment for patients with KIT exon 9 mutation is imatinib 800 mg daily [III, B; ESCAT score: I-A].
- Standard first-line treatment for patients with PDGFRA exon 18 D842V mutations is avapritinib 300 mg daily [III, A; ESMO-MCBS v1.1. score: 3; ESCAT score: I-B].
- NTRK-re-arranged GISTs are sensitive to treatment with NTRK inhibitors [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C].
- BRAF-mutated GISTs benefit from BRAF inhibitors (including BRAF MEK inhibitor combinations) [V, B; ESCAT score: III-A].

Table 1. Personalised medicine synopsis

Biomarker	Method	Use	LoE	GoR
Mitotic index	Pathology	Disease classification Prognostic relevance Used for medical treatment decisions	IV	A
KIT mutations	Sanger sequencing or NGS	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions Currently actionable/targetable	I	A
PDGFRA mutations	Sanger sequencing or NGS	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions Currently actionable/targetable	I/III	A
NTRK mutations	Sanger sequencing or NGS	Disease classification Predictive relevance Used for medical treatment decisions Currently actionable/targetable	III	A
BRAF mutations	Sanger sequencing or NGS	Disease classification Predictive relevance Used for medical treatment decisions Currently actionable/targetable	V	B
SDH mutations/epimutations	IHC	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions	I	A

GoR, grade of recommendation; IHC, immunohistochemistry; LoE, level of evidence; NGS, next generation sequencing; PDGFRA, platelet-derived growth factor receptor alpha; SDH, succinate dehydrogenase.

ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
Mélanome	
NCCN – Mélanome [NCCN, 2022c]	***Melanoma: Cutaneous – Version 2.2022*** (January 26 2022) PRINCIPLES OF MOLECULAR TESTING Specific mutations • BRAF, NRAS, KIT) and implications ▪ BRAF (B-Raf proto-oncogene) mutations: ○ BRAF is a serine threonine kinase that activates the mitogen-activated kinase pathway. Mutations in this gene lead to unrestrained cell growth and proliferation. ○ Some clinical features are associated with a higher frequency of BRAF mutations (eg, intermittent sun-exposed skin, younger age, trunk location), but these should not be used either as a proxy for these mutations or to decide testing. ○ BRAF mutations are most commonly found in the 600th codon (V600), most frequently V600E (80%) but also including V600K (15%) and V600R/M/D/G (5%). • BRAF V600 mutations are associated with sensitivity to BRAF inhibitors. Available evidence suggests that BRAF inhibitors should not be used in patients without BRAF V600 mutations. • BRAF V600 mutations are also associated with sensitivity to MEK inhibitors. • Clinical trials have shown that the combination of BRAF and MEK inhibitors are superior to either agent alone in patients with BRAF V600 mutations. • Extensive clinical trial data have shown that compared with BRAF V600E, patients with BRAF V600K-mutated metastatic melanoma may have slightly lower response/benefit when treated with BRAF ± MEK inhibitors. Less frequent mutations affecting codon 600 (including V600R/M'/D/G) also may benefit from these therapies. ▪ BRAF mutations outside of the 600th codon (BRAF non-V600 mutations) and BRAF fusions are also found in approximately 5% of melanomas. ○ Mutations in codons near V600 in exon 15 (specifically BRAF L597 and BRAF K601) have shown response to MEK inhibitors and BRAF and MEK inhibitor combinations. ○ Fusions in BRAF have also shown response to MEK inhibitors and non-specific RAF inhibitors (eg sorafenib). ○ Mutations in other codons in exon 11 or exon 15 have not demonstrated response to either BRAF or MEK inhibitors. ▪ KIT (proto-oncogene c-KIT) mutations ○ KIT is a receptor tyrosine kinase that promotes cell growth and proliferation. ○ KIT mutations are present in 10%–15% of melanomas of mucosal (most frequently vulvovaginal primaries, but also anorectal and sinonasal) and acral (ie, non–hair-bearing surfaces of palms and soles, nailbeds) origin. They are also present on 2%–3% of chronically sun-exposed skin, but extremely rarely on skin with intermittent sun exposure. Thus, clinical features can guide the decision whether to perform KIT mutation testing. • KIT mutations may occur in multiple "hotspots" across the gene and differ in their sensitivity to KIT inhibitors (eg, imatinib, sunitinib, nilotinib). • KIT exon 11 and exon 13 mutations (eg, W557, V559, L576P, K642E) appear to have a high level of sensitivity to KIT inhibition. • KIT exon 17 mutations (eg, D816H) appear to have minimal or no sensitivity to KIT inhibitors. • KIT amplifications appear to have minimal or no sensitivity to KIT inhibitors. ▪ NRAS (NRAS proto-oncogene) mutations ○ NRAS is a GTPase that activates mitogen-activated protein kinase signaling and other signaling pathways, leading to cell growth and proliferation.

ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
	○ NRAS mutations appear to correlate with poor survival in localized and advanced melanoma. ○ NRAS mutations are present in approximately 15% of melanomas in skin with chronic and intermittent sun exposure, acral surfaces, and mucosal surfaces. ○ MEK inhibitors may produce responses in a minority of patients with NRAS mutations ○ Given the low probability of overlapping targetable mutations (including BRAF and KIT mutations), the presence of an NRAS mutation may identify patients who will not benefit from additional molecular testing. Indications for genetic testing ▪ The panel does not recommend BRAF or NGS testing for resected stage I–II cutaneous melanoma unless it will inform clinical trial ▪ participation. ▪ BRAF mutation testing is recommended for patients with stage III at high risk for recurrence for whom future BRAF-directed therapy may be an option. ▪ For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in BRAF, and in the appropriate clinical setting, KIT from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (eg, larger NGS panels, BRAF non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. ▪ If BRAF single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (eg, KIT, BRAF non-V600).
ESMO [Michielin *et al.*, 2019]	***Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*** (Dec 2019) <u>Molecular characterisation</u> ▪ Mutation testing for actionable mutations is mandatory in patients with resectable or unresectable stage III or stage IV [I, A], and is highly recommended in high-risk resected disease stage IIC but not for stage I or stage IIA–IIB. BRAF testing is mandatory [I, A]. ▪ If the tumour is BRAF wild-type (WT) at the V600 locus (class I BRAF mutant) sequencing the loci of the other known minor BRAF mutations (class II and class III BRAF mutant) to confirm WT status and testing for NRAS and c-kit mutations are recommended [II, C] [14]. Although no good targeted therapies options exist for these drivers at the moment, they are important to identify for future opportunities and to select patients for clinical trials. ▪ The main melanoma subtypes are associated with different mutational landscapes: frequently mutated genes include: ○ BRAF, CDKN2A, NRAS and TP53 in cutaneous melanoma, ○ BRAF, NRAS, NF1 and KIT in acral melanoma (though with lower frequencies than in cutaneous melanoma), ○ SF3B1 in mucosal melanoma. <u>Management of advanced/metastatic disease</u> ▪ Patients with metastatic melanoma should have metastasis (preferably) or the primary tumour screened for detection of BRAF V600 mutation treatment options for the first- and second-line settings include anti-PD-1 antibodies (pembrolizumab, nivolumab), PD-1 and ipilimumab for all patients, and BRAFi/MEKi combination for patients with BRAF-mutated melanoma [II, B] ▪ For BRAF WT disease, second-line options are very limited and inclusion in clinical trials and/or personalised approaches could be discussed. If the firstline treatment was anti-PD-1 alone, ipilimumab is an option [II, B] as well as ipilimumab/nivolumab [IV, B] ▪ For BRAF-mutated disease, all the options available for WT melanoma are still valid with the addition of BRAFis/MEKis if not used in the first-line setting ▪ For NRAS-mutated melanoma, due to the limited efficacy of MEK inhibitors, first-line immunotherapy options identical to those of WT melanoma are the first choice

ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
Cancer de la tyroïde	
NCCN – Thyroid Carcinoma [NCCN, 2021a]	***Thyroid Carcinoma – Version 3.2021*** (October 15 2021) ▪ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate. ▪ Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive], dabrafenib [BRAF positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate. FNA Results Molecular diagnostic testing to detect individual mutations (eg, BRAF, V600E, RET/PTC, RAS, PAX8/PPAR gamma) or pattern recognition approaches using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate to assist in management decisions. Tumor Variables Affecting Prognosis In patients with sporadic medullary carcinoma, a somatic RET oncogene mutation confers an adverse prognosis. Papillary carcinoma Modified: For advanced, progressive, or threatening disease, genomic teste to identify actionable mutations (including ALK, NTRK, and RET gene fusions) DNA mismatch repair (dMMR), microsatellite instability (MSI), and tumor mutational burden (TMB). Anaplastic thyroid carcinoma (ATC) ▪ Molecular testing should include BRAF, NTRK, ALK, RET, MSI, dMMR, and tumor mutational burden.
CAP [Chiosea *et al.*, 2017]	***Template for reporting results of biomarker testing of specimens from patients with thyroid carcinoma*** (April 9 2021) B. BRAF Mutational Analysis The presence of BRAF V600E mutation in a fine-needle aspirate is indicative of about 99% risk of cancer in the sampled thyroid nodule. When identified alone, BRAF V600E mutation may merely reflect the conventional morphology or tall cell variant of papillary thyroid carcinoma. The combination of BRAF V600E mutation with TERT, AKT1, PIK3CA, or TP53 mutations predicts a more aggressive tumor behavior.6-12 BRAF K601E is an unusual BRAF mutation, which had been reported in follicular variant of papillary thyroid carcinoma and rarely in follicular adenomas. C. RAS Mutational Analysis The finding of RAS mutation in a fine-needle aspirate is associated with an about 80% risk of cancer in a given nodule. The most common types of cancer with RAS mutations are the encapsulated follicular variant of papillary carcinoma and follicular carcinoma. The remaining RAS-positive thyroid nodules are usually diagnosed as follicular adenomas. Sporadic medullary thyroid carcinomas with wild type RET genes may harbor RAS mutations (HRAS or KRAS). F. RET Mutational Analysis The presence of RET rearrangements in thyroid fine-needle aspirate is associated with >95% risk of cancer, most frequently classic papillary thyroid carcinoma. Mutations of the RET gene are typically present in sporadic and familial forms of medullary thyroid carcinoma. Among sporadic medullary carcinomas, RET p.M918T mutation accounts for more than 75% of all somatic RET mutations found in medullary carcinomas.

<table>
<tr><th>ORGANISATIONS,
[AUTEUR, ANNÉE]
HYPERLIEN</th><th>TITRE DU DOCUMENT (DATE DE PUBLICATION)
RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT</th></tr>
<tr><td></td><td>Laboratories should disclose whether the test was performed on tissue type (tumor versus normal tissue) that allows distinguishing between germline (inherited) and sporadic (acquired) mutation. Nevertheless, the distinction between sporadic and germline mutation can be reliably made only by testing a nontumorous specimen, preferably patient blood. Clinical management of patients based on the presence of specific RET mutations has been defined.</td></tr>
<tr><td>ESMO

[Filetti et al., 2019]</td><td>Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2016 Sep 28)

Table 1. WHO classification for differentiated follicular-derived thyroid carcinomas: morphological parameters and molecular markers
<table><tr><th>Tumour type</th><th>Morphology</th><th>Molecular markers</th></tr><tr><td>NIFTP</td><td>Encapsulated, clear nuclei, no papillae</td><td>RAS, BRAF K601E</td></tr><tr><td>Papillary carcinoma</td><td></td><td></td></tr><tr><td>Classical</td><td>Papillae and clear nuclei</td><td>BRAF V600E, RET/PTC fus, NTRK fus, ALK fus, 1q amp</td></tr><tr><td>Follicular variant</td><td>Follicles and clear nuclei</td><td>BRAF K601E, RAS, PAX8/PPARγ, EIF1AX, THADA fus, 22q del</td></tr><tr><td>Tall, columnar, solid, hobnail variants</td><td>Special structural and cell features</td><td>BRAF V600E, 1q amp, TERT promoter, TP53, PIK3CA, CTNNB1</td></tr><tr><td>Follicular carcinoma</td><td>Capsular invasion (MI), vascular invasion >4 blood vessels (angioinvasive), extrathyroidal invasion (WI)</td><td>RAS, PAX8/PPARγ, PTEN, PIK3CA, TSHR, TERT promoter, CNA</td></tr><tr><td>Hürthle cell carcinoma</td><td>Capsular invasion (MI), vascular invasion >4 blood vessels (WI)</td><td>RAS, EIF1AX, PTEN, TP53, CNA, mtDNA</td></tr><tr><td>Poorly differentiated carcinoma</td><td>Invasion, mitoses >3, necrosis, convoluted nuclei</td><td>RAS, TERT promoter, TP53, PIK3CA, PTEN, CTNNB1, AKT1, EIF1AX, ALK fus, histone methyltransferases, SWI/SNF chromatin remodelling complex</td></tr></table>amp, amplification; CNA, copy number alteration; del, deletion; fus, fusion; MI, minimally invasive; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; SWI/SNF, switch/sucrose non-fermentable; WHO, World Health Organization; WI, widely invasive.</td></tr>
<tr><td colspan="2">Carcinome urothéliale</td></tr>
<tr><td>NCCN – Bladder cancer

[NCCN, 2022d]</td><td>Bladder Cancer – Version 1.2022 (February 11 2022)

<u>Muscle Invasive Bladder Cancer</u>
Consider molecular/genomic testing. Molecular/genomic testing in a CLIA-approved laboratory, including FGFR RQG RT-PCR for FGFR3 or FGFR2 genetic alterations.

<u>Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum or post-checkpoint inhibitor).</u>
Participation in clinical trials of new agents is recommended.
▪ Erdafinib (Only for patients with susceptible FGFR3 or FGFR2 genetic alterations).</td></tr>
</table>

Tableau E-2 Données extraites des documents publiés par des agences règlementaires, autorités de santé et sociétés savantes – volet économique

AUTEURS (PAYS)	DEVIS, APPROCHE ANALYTIQUE, PERSPECTIVE, HORIZON TEMPOREL, TAUX D'ACTUALISATION	POPULATION	INTERVENTION ET COMPARATEUR, ISSUES	RÉSULTATS ET CONCLUSION
CANCER DU POUMON				
Schluckebier *et al.*, 2020 (Brésil)	Devis : ACU/ACE Approche analytique : arbre décisionnel/microsimulation Perspective : assureurs privés brésiliens Horizon temporel : 5 ans (à vie pour la microsimulation) Taux d'actualisation : 5 %	Patients adultes atteints d'un CPNPC (adénocarcinome) de stade 4	**Stratégie 1** : *EGFR* (RT-PCR) → *ALK* (FISH) → *ROS1* (FISH). **Stratégie 2** : *EGFR* (RT-PCR) → *ALK* et *ROS1* (FISH) simultanément. **Stratégie 3** : *EGFR*, *ALK* et *ROS1* (NGS) simultanément. Issues : ▪ Coûts diagnostic moléculaire et de traitement ($ US 2017); ▪ Nombre de cas adéquatement diagnostiqué; ▪ Années de vie gagnées; ▪ QALY.	**RCED :** **Stratégie 3 c. 2** : 4 921,09 $/cas additionnel adéquatement détecté. **Stratégie 2 c. 1** : 1 359,96 $/ cas additionnel adéquatement détecté. **RCED** incluant les données de survie globale et d'efficacité des traitements (microsimulation) de la **stratégie 3 c. 2** est de 302 696 $/QALY gagné. La probabilité que le **NGS** soit une stratégie de détection coût-efficace est faible (40 %) **c. stratégie 2** et ce pour une propension à payer qui est, selon les auteurs, généralement acceptée.
Tan *et al.*, 2020 (Singapour)	Devis : ACE Approche analytique : arbre décisionnel Perspective : système de soins de santé Horizon temporel : moins d'un an Taux d'actualisation : aucun	Patients atteints d'un CPNPC non épidermoïde nouvellement diagnostiqué et non préalablement traité (n=174). ACE réalisée chez sous-groupe adénocarcinome de stade IV; n=104)	Intervention : panel NGS (29 gènes + *ALK*/*ROS1*/*MET*) **Stratégie 1** (singleplex) : *EGFR* → NGS+PD-L1 **Stratégie 2** (multiplex) : Dx routine → NGS **Stratégie 3** (NGS) : NGS + PD-L1. Comparateur (**stratégie 4**): Dx routine *EGFR* (RT-PCR, Sanger), *ALK, ROS1, MET, RET* (FISH) et PD-L1 (IHC). Issues : ▪ Coûts : SG $2018 ▪ Pourcentage additionnel de patients éligibles à une thérapie ciblée c.-à-d. avec une altération dans *BRAF, EGFR, HER2, ALK, RET, ROS1* et PD-L1.	**Stratégie 1 et 3** dominant c. **stratégie 4** **Stratégie 3** c. **stratégie 1** : RCED 113 $/pourcentage de patient additionnel admissible à une thérapie ciblée. **Stratégie 2** c. **stratégie 3**, RCED : 267 $/pourcentage de patient additionnel admissible à une thérapie ciblée.

AUTEURS (PAYS)	DEVIS, APPROCHE ANALYTIQUE, PERSPECTIVE, HORIZON TEMPOREL, TAUX D'ACTUALISATION	POPULATION	INTERVENTION ET COMPARATEUR, ISSUES	RÉSULTATS ET CONCLUSION
Pennell *et al.*, 2019 (États-Unis) (Novartis)	Devis : ACE Approche analytique : arbre décisionnel Perspective : Centers for Medicare & Medicaid Services (CMS) et payeur de soins. Le modèle tient compte des coûts associés aux tests uniquement et excluent les coûts encourus en aval. Horizon temporel : s.o. Taux d'actualisation : s.o.	Patients atteints d'un CPNPC métastatique nouvellement diagnostiqué et admissibles à un test génomique. Cohorte hypothétique de 1M de membres, âgés de 65 ans et plus si perspective Medicare, ou entre 18 et 65 ans pour perspective d'assureurs privés.	Toutes les stratégies incluent PD-L1 (IHC) : **Stratégie 1** : NGS : panel pour toutes les altérations (simultanément), avec ou sans traitement approuvé par la FDA : *EGRF, ALK, ROS1, BRAF, MET, HER2, RET, NTRK1* **Stratégie 2** : Tests séquentiels de gènes uniques : altérations avec traitement approuvé par FDA : *EGFR, ALK, ROS1 et BRAF*. Si négatif, tests séquentiels de gènes uniques ou NGS pour altérations sans traitement approuvé par la FDA : *MET, HER2, RET, NTRK1*. **Stratégie 3**: Tests d'exclusion: *KRAS* → tests séquentiels **Stratégie 4 :** Hotspot panel : tests simultanés pour altérations avec thérapie approuvée par la FDA (*EGFR, ALK, ROS1, BRAF*). Si négatif, tests séquentiels de gène unique ou NGS pour altérations sans traitement approuvé par la FDA : *MET, HER2, RET, NTRK1*. Issues : ▪ Coûts : $ US 2017; ▪ Coûts des tests; ▪ Délai de réponse/temps de traitement; ▪ Proportion de patients avec thérapie approuvée ou non par la FDA.	**Stratégie 1 c. stratégies2, 3 et 4** : ↓ des coûts d'analyse de 1,97 à 3,03 M$ pour la cohorte Medicare (2 066 patients) et de 5 400 $ à 354 800 $ pour la cohorte de payeurs privés (156 patients). **Stratégie 1** identifie 2,3 % et 5,9 % plus de patients avec une mutation dans un gène visé par une thérapie ciblée approuvée par la FDA que les stratégies 2 et 3, respectivement. Le taux de détection de la stratégie 4 est le même que le NGS. Concernant les altérations pour lesquelles il n'y a pas de thérapie ciblée, la **stratégie 1** permet d'identifier de 36,1 % à 43,7 % plus de patients que les trois autres stratégies, et ce, dans des délais plus courts (stratégies 1 et 2 : 2 semaines; stratégie 3 : 2,7 semaines; stratégie 4 : 2,8 semaines).
Steuten *et al.*, 2019 (États-Unis)	Devis : ACE Approche analytique : arbre décisionnel Perspectives : payeur de soins Horizon temporel : à vie Taux d'actualisation : 3 %	Patients de tout âges diagnostiqués avec CPNPC avancé (stade IIIB ou IV) ou récidivant/progressif, ayant reçu au moins une ligne de traitement (n=5 688).	Intervention : MGPS (panel NGS de ≥ 30 gènes) Comparateur : SMGT (tests de gène unique [FISH, PCR, tests maisons] ou panel NGS de < 30 gènes); Issues : ▪ Coûts médicaux directs: $ US 2017; ▪ Années de vie (LY)	MGPS c. SMGT : ▪ RCED : 210 017 $/ année de vie gagnée (↑ coûts de 12 467 $ et ↑ de 0,06 année de vie); ▪ Pour une propension à payer de 212 170 $ (150 000 ($ US 2017)/ année de vie gagnée, la probabilité d'être efficient est de 52 %.

AUTEURS (PAYS)	DEVIS, APPROCHE ANALYTIQUE, PERSPECTIVE, HORIZON TEMPOREL, TAUX D'ACTUALISATION	POPULATION	INTERVENTION ET COMPARATEUR, ISSUES	RÉSULTATS ET CONCLUSION
				MGPS identifie une mutation actionnable chez 30,1 % des patients (*EGFR, ALK, ROS, BRAF, MET, ERBB2*, etc.) et 21,4 % ont reçu une thérapie ciblée comparativement à 23,3 % et 18,7 %, respectivement, pour le SMGT.
Yu *et al.*, 2018 (États-Unis)	Devis : ACE Approche analytique : modèle de Markov Perspective : payeur de soins Horizon temporel : 5 ans, cycle mensuel Actualisation: s.o.	Cohorte hypothétique de 1 million de patients atteints d'un CPNPC non squameux de grade avancé nouvellement diagnostiqué.	Intervention : NGS panel *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *HER2* et *RET* Comparateur : tests en séquence de gènes uniques actionnables pour thérapie ciblée : *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *HER2* et *RET* Issues : ▪ Coûts : $ US (2017) ▪ Coûts de traitement ▪ Coûts par résultat positif	NGS c. tests gènes uniques en séquence : ▪ ↓ coûts d'analyse de 34 868 $ ▪ Identifie 30,0 % de patients avec une mutation dans un gène actionnable ou en émergence c. à 19,5 %. ▪ Stratégie dominante : ↓ coûts d'environ 1 834 $ par cas positif additionnel détecté.
AUTRES CANCERS				
Li *et al.*, 2015 (États-Unis)	Devis : ACU Approche analytique : arbre décisionnel et modèle de survie partitionnée (cycle de 3 mois) Perspective : payeur de soins de santé Horizon temporel : 2 ans Taux d'actualisation : 3 % (coûts seulement)	Patients atteints d'un mélanome au stade métastatique.	Intervention : panel SNG OncoVantage[MC] (34 gènes associés au développement de cancer, dont *BRAF* et *KIT*). Comparateur : test cobas 4800 *BRAF V600* Issues : ▪ Coûts par patient ($ US, année non précisée), incluant les coûts de traitement ▪ QALY	NGS c. au test unique sur *BRAF* : ↓ coûts de US$ 8 943 et ↑de 0,0174 QALY sur 2 ans. Résultats demeurent robustes dans les analyses de sensibilité.

Abréviations : ACE : Analyse coût-efficacité; ACU : analyse coût-utilité; CPNPC : Cancer du poumon non à petites cellules; FDA : Food and drug administration; FISH : Fluorescence in situ hybridization; LY : Life year; MGPS : Multi-gene panel sequencing; NGS : Next generation sequencing; RT-PCR : Reverse transcription polymerase chain reaction; RCED : Ratio coût-efficacité différentiel; s.o. : Sans objet; SMGT : Single-marker genetic testing

→ : si négatif; ↓ : diminution; ↑ : augmentation

Les coûts ont été convertis en dollars canadien 2018 en fonction de la parité du pouvoir d'achat (OCDE) puis indexé en dollars canadien 2022. Les conversions ont été réalisées en fonction de la parité des pouvoirs d'achat à l'aide de l'outil CCEMG EPPI – Centre *cost converter*, disponible à : https://eppi.ioe.ac.uk/costconversion/default.aspx.
Lorsque nécessaire, l'indice des prix à la consommation (IPC) concernant le Québec a été utilisé pour actualiser les coûts à l'année en cours au moment de la rédaction (2022). L'IPC en vigueur pour le Québec est disponible à : https://statistique.quebec.ca/fr/document/indice-prix-consommation-ipc/tableau/indice-des-prix-a-la-consommation-ipc-indice-ensemble-canada-quebec-rmr-montreal-quebec-donnees-mensuelles-non-desaisonnalisees.

ANNEXE F

Évaluation de la qualité méthodologique des publications sélectionnées

Tableau F-1 Évaluation de la qualité méthodologie des publications sélectionnées – volet clinique (AGREE II)

ÉTUDE	SCORE ATTRIBUÉ EN FONCTION DES CRITÈRES D'ÉVALUATION CONSIDÉRÉS						SCORE GLOBAL	QUALITÉ GLOBAL*
	Champ d'application et objectifs	Participation des groupes concernés	Rigueur du processus d'élaboration du guide	Clarté et présentation	Applicabilité	Indépendance éditoriale		
Mosele *et al.*, 2020	61,1 %	44,4 %	16,7 %	83,3 %	25,0 %	75,0 %	41,3 %	Faible
INESSS et GÉOQ, 2022	66,7 %	61,1 %	29,2 %	83,3 %	41,7 %	100,0 %	53,6 %	Modérée
Lindeman *et al.*, 2018	83,3 %	38,9 %	70,8 %	83,3 %	33,3 %	100,0 %	65,9 %	Modérée
Planchard *et al.*, 2020	27,8 %	38,9 %	25,0 %	83,3 %	16,7 %	100,0 %	39,9 %	Faible
NCCN, 2022a	27,8 %	61,1 %	25,0 %	88,9 %	25,0 %	50,0 %	40,6 %	Faible
INESSS et GÉOQ, 2016a; INESSS et GÉOQ, 2016b	55,6 %	44,4 %	33,3 %	77,8 %	16,7 %	16,7 %	39,1 %	Faible
Sepulveda *et al.*, 2017	100,0 %	61,1 %	62,5 %	83,3 %	12,5 %	100,0 %	64,5 %	Modérée
Van Cutsem *et al.*, 2016	50,0 %	44,4 %	25,0 %	83,3 %	12,5 %	100,0 %	42,8 %	Faible
NCCN, 2022b	27,8 %	44,4 %	25,0 %	88,9 %	25,0 %	50,0 %	38,4 %	Faible
GGPO, 2019	94,4 %	83,3 %	52,1 %	88,9 %	29,2 %	100,0 %	66,7 %	Modérée
NCCN, 2021b	27,8 %	44,4 %	25,0 %	88,9 %	25,0 %	50,0 %	38,4 %	Faible
Casali *et al.*, 2022	27,8 %	38,9 %	25,0 %	83,3 %	16,7 %	100,0 %	39,9 %	Faible
NCCN, 2022c	27,8 %	61,1 %	25,0 %	88,9 %	25,0 %	50,0 %	40,6 %	Faible
Michielin *et al.*, 2019	27,8 %	38,9 %	25,0 %	83,3 %	16,7 %	100,0 %	39,9 %	Faible
NCCN, 2021a	27,8 %	44,4 %	25,0 %	88,9 %	25,0 %	50,0 %	38,4 %	Faible
Filetti *et al.*, 2019	27,8 %	38,9 %	25,0 %	83,3 %	16,7 %	100,0 %	39,9 %	Faible
NCCN, 2022d	27,8 %	44,4 %	25,0 %	88,9 %	25,0 %	50,0 %	38,4 %	Faible

Études non-retenues pour l'évaluation de la qualité : Wu *et al.*, 2019; Kalemkerian *et al.*, 2018; Yoshino *et al.*, 2018; Cancer Council Australia, 2017; Chiosea *et al.*, 2017; Bartley *et al.*, 2014.

* Les publications sont jugées de bonne qualité méthodologique avec un score global fixé arbitrairement à 75 % ou plus; de qualité modérée avec un score global de 50 % à 74 %; de faible qualité avec un score global de 25 % à 49 %; et de très faible qualité avec un score global de moins de 25 %.

Tableau F-2 Évaluation de la qualité méthodologie des études économiques (grille CASP)

Publication	Schluckebier 2020	Tan 2020	Pennell 2019	Steuten 2019	Yu 2018	Li 2015
1- L'évaluation repose-t-elle sur une question bien définie ?	Oui	Oui	Oui	Oui	Oui	Oui
2- A-t-on fait une description complète des alternatives comparées ?	Oui	Oui	Oui	Oui	Oui	Oui
3- L'article démontre-t-il l'efficacité de l'intervention ? (l'innocuité de l'intervention est-elle acceptable ?)	Oui	Oui	Partiellement	Oui	Partiellement	Oui
4- Les effets de l'intervention ont-ils été identifiés, mesurés et évalués adéquatement ?	Oui	Oui	Oui	Oui	Oui	Oui
5- A-t-on identifié, mesuré avec les unités appropriées et évalué de façon vraisemblable toutes les ressources et tous les coûts importants et pertinents pour chaque alternative considérée ?	Non	Difficile à dire	Non	Difficile à dire	Oui	Oui
6- Les auteurs ont-ils ajusté les coûts et les conséquences en fonction du moment où ils se concrétiseront (actualisation) ?	Oui	Non	Non rapporté	Oui	Non rapporté	Oui (coûts seulement)
7- Quels sont les résultats de l'évaluation ?	SNG ne serait pas coût-efficace	SNG seul et Singleplex sont coût-efficace	SNG serait une stratégie moins coûteuse et permettrait d'identifier plus de patients	SNG serait « modérément » coût-efficace.	SNG serait plus dispendieux et permettrait d'identifier plus de patients	SNG serait coût-efficace
8- Une analyse différentielle des conséquences et du coût a-t-elle été réalisée pour les alternatives comparées ?	Oui	Oui	Non	Oui	Non	Oui
9- Une analyse de sensibilité en bonne et due forme a-t-elle été effectuée ?	Oui, probabiliste	Non	Partiellement, univariée	Oui	Partiellement, univariée et scénarios	Oui
10- Le modèle aura-t-il la même efficacité dans le contexte québécois ?	Difficile à dire	Difficile à dire	Difficile à dire	Difficile à dire	Difficile à dire	Difficile à dire
11- Les coûts sont-ils transposables au contexte québécois ?	Non	Non	Non	Non	Non	Non
12- L'utilisation du même modèle dans le contexte québécois est-elle justifiée ?	Non	Non	Non	Non	Non	Non

ANNEXE G

Données économiques supplémentaires

Tableau G-1 Impact brut – *statu quo*

	Cibles moléculaires	AN 1	AN 2	AN 3	TOTAL
1	EGFR-ALK-ROS1	1 819 428 $	1 819 428 $	1 819 428 $	5 458 284 $
2	EGFR-ALK-ROS1-NTRK	2 798 036 $	2 798 036 $	2 798 036 $	8 394 109 $
3	EGFR-ALK-ROS1-NTRK-BRAF	3 242 858 $	3 242 858 $	3 242 858 $	9 728 575 $
4	EGFR-ALK-ROS1-NTRK-BRAF-KRAS	3 830 023 $	3 830 023 $	3 830 023 $	11 490 070 $
5	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET	4 417 188 $	4 417 188 $	4 417 188 $	13 251 565 $
6	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET-RET	5 395 797 $	5 395 797 $	5 395 797 $	16 187 390 $
7	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET-RET-HER2	6 374 405 $	6 374 405 $	6 374 405 $	19 123 216 $

Tableau G-2 Nouveau scenario: Ajout du Focus Panel[MC]

	Cibles moléculaires	AN 1	AN 2	AN 3	TOTAL
1	EGFR-ALK-ROS1	2 195 250 $	2 345 578 $	2 495 907 $	7 036 735 $
2	EGFR-ALK-ROS1-NTRK	2 684 554 $	2 639 161 $	2 593 768 $	7 917 482 $
3	EGFR-ALK-ROS1-NTRK-BRAF	2 906 965 $	2 772 607 $	2 638 250 $	8 317 822 $
4	EGFR-ALK-ROS1-NTRK-BRAF-KRAS	3 200 547 $	2 948 757 $	2 696 966 $	8 846 270 $
5	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET	3 494 130 $	3 124 906 $	2 755 683 $	9 374 719 $
6	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET-RET	3 983 434 $	3 418 489 $	2 853 544 $	10 255 467 $
7	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET-RET-HER2	4 472 738 $	3 712 071 $	2 951 405 $	11 136 214 $

Tableau G-3 Impact net

	Cibles moléculaires	AN 1	AN 2	AN 3	TOTAL
1	EGFR-ALK-ROS1	375 822 $	526 150 $	676 479 $	1 578 451 $
2	EGFR-ALK-ROS1-NTRK	-113 483 $	-158 876 $	-204 269 $	-476 627 $
3	EGFR-ALK-ROS1-NTRK-BRAF	-335 894 $	-470 251 $	-604 608 $	-1 410 753 $
4	EGFR-ALK-ROS1-NTRK-BRAF-KRAS	-629 476 $	-881 267 $	-1 133 057 $	-2 643 800 $
5	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET	-923 059 $	-1 292 282 $	-1 661 505 $	-3 876 846 $
6	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET-RET	-1 412 363 $	-1 977 308 $	-2 542 25 $	-5 931 924 $
7	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET-RET-HER2	-1 901 667 $	-2 662 334 $	-3 423 001 $	-7 987 001 $

Tableau G-4 Impact net – Analyses de sensibilité

	Cibles moléculaires	Parts SNG 40, 60 et 80 %	Parts SNG : 60, 80 et 100 %	Population admissible (-5 %)	Population admissible (+5 %)
1	EGFR-ALK-ROS1	1 352 958 $	1 803 944 $	1 499 528 $	1 657 373 $
2	EGFR-ALK-ROS1-NTRK	-408 537 $	-544 716 $	-452 795 $	-500 458 $
3	EGFR-ALK-ROS1-NTRK-BRAF	-1 209 217 $	-1 612 289 $	-1 340 215 $	-1 481 291 $
4	EGFR-ALK-ROS1-NTRK-BRAF-KRAS	-2 266 114 $	-3 021 485 $	-2 511 610 $	-2 775 990 $
5	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET	-3 323 011 $	-4 430 681 $	-3 683 004 $	-4 070 688 $
6	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET-RET	-5 084 506 $	-6 779 341 $	-5 635 328 $	-6 228 520 $
7	EGFR-ALK-ROS1-NTRK-BRAF-KRAS-MET-RET-HER2	-6 846 001 $	-9 128 001 $	-7 587 651 $	-8 386 351 $

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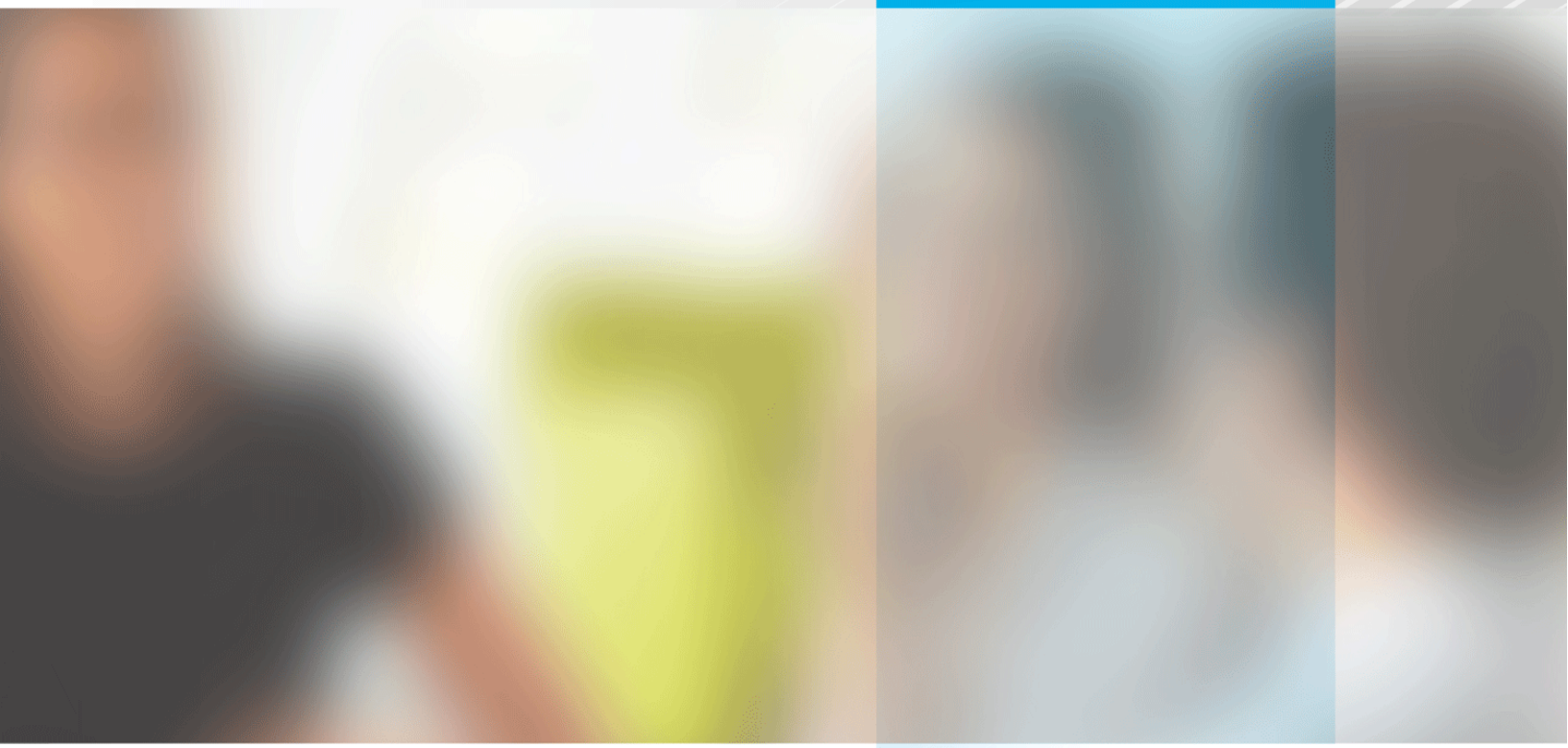

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