Découvertes de hasard et examens systématiques

Altération des tests hépatiques chez un patient asymptomatique

Cas 1

- Patient de 65 ans, diabétique, ancien fumeur, passant un examen de dépistage
- La biologie sanguine montre :
  - sGOT : 54 U/ml (N<47)
  - sGPT : 65 U/ml (N<49)
- Que faire ?

1. Confirmer

- Un bilan sera envisagé si la persistance de l'altération des tests hépatiques (élévation des transaminases) est confirmée.

2. Si confirmé : bilan

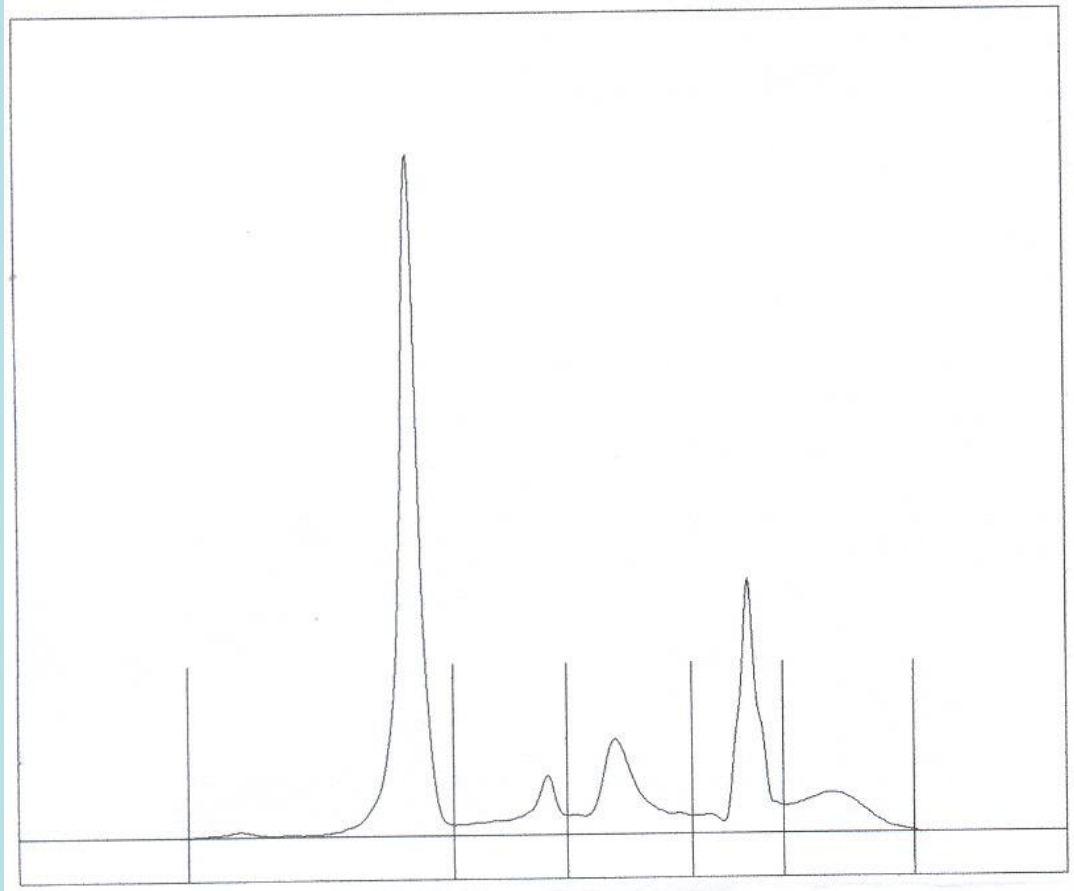
1. **anamnèse et examen physique** (insister sur les médicaments pris par le patient)
2. **recherche d'une maladie hépatique** :
   -échographie hépatique et, en cas de doute, CT scan ou RMN
   -exclure trouble de la synthèse et de l'excrétion hépatique : PTT, albumine, bilirubine
   - tests spécifiques :
   * hépatite chronique B et C : sérologie virale
   * hémochromatose: fer sérique, ferritine, saturation
   * maladies auto-immunes : facteurs anti-nucléaires, anticorps anti-mitochondries, anticorps anti-muscles lisses, dosage des immunoglobulines …
   * déficit en α1 anti-trypsine
   * maladie de Wilson : céruloplasmine, dosage du cuivre sérique
3. **exclure des causes non-hépatiques** à l'élévation des transaminases :
   -maladie thyroïdienne : dosage de la TSH
   -maladie cœliaque : recherche des anticorps contre l'endomysium
   -pathologie musculaire : dosage des CPK

Principale pathologie hépatique en cause

de loin le plus fréquent est la stéatose hépatique non alcoolique (associée à l'obésité et autres facteurs du syndrome dit métabolique) avec risque d'évolution vers la fibrose, la cirrhose et hépatocarcinome

Gammopathie monoclonale de signification incertaine (MGUS)

Que faire si on observe une telle électrophorèse chez une patiente asymptomatique de 57 ans ?



Fraction	Rel %	g/
ALBUMINE	49.4 -	
ALPHA1	7.5	
ALPHA2	14.6 +	
BETA	19.0 +++	
GAMMA	9.6 -	

Reference Ranges

	Rel %	g
ALBUMINE	52.8 - 63.2	
ALPHA1	4.2 - 9.0	
ALPHA2	8.0 - 13.7	
BETA	7.7 - 13.4	
GAMMA	9.7 - 18.2	

Risque

risque = 1%/an de transformation en myélome

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Follow-up of Monoclonal Gammopathy of Undetermined Significance

Robert A. Kyle, M.D., Dirk R. Larson, M.S., Terry M. Therneau, Ph.D., Angela Dispenzieri, M.D., Shaji Kumar, M.D., James R. Cerhan, M.D., Ph.D., and S. Vincent Rajkumar, M.D.

ABSTRACT

BACKGROUND

Monoclonal gammopathy of undetermined significance (MGUS) occurs in approximately 3% of persons 50 years of age or older.

METHODS

We studied 1384 patients who were residing in southeastern Minnesota and in whom MGUS was diagnosed at the Mayo Clinic in the period from 1960 through 1994; the median follow-up was 34.1 years (range, 0.0 to 43.6). The primary end point was progression to multiple myeloma or another plasma-cell or lymphoid disorder.

From the Divisions of Hematology (R.A.K., A.D., S.K., S.V.R.), Biostatistics (D.R.L., T.M.T.), and Epidemiology (J.R.C.), Mayo Clinic, Rochester, MN. Address reprint requests to Dr. Kyle at the Division of Hematology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at kyle.robert@mayo.edu.

N Engl J Med 2018;378:241-9.
DOI: 10.1056/NEJMoa1709974

1.384 patients

- Le risque de progression est de 10% à 10 ans, 18% à 20 ans, 28% à 30 ans, 36% à 35 ans et 36% à 40 ans.
- Les patients atteints de MGUS ont une survie plus courte que celle attendue dans la population témoin de résidents du Minnesota d'âge et de sexe appariés (médiane: 8,1 vs 12,4 ans; p <0,001).

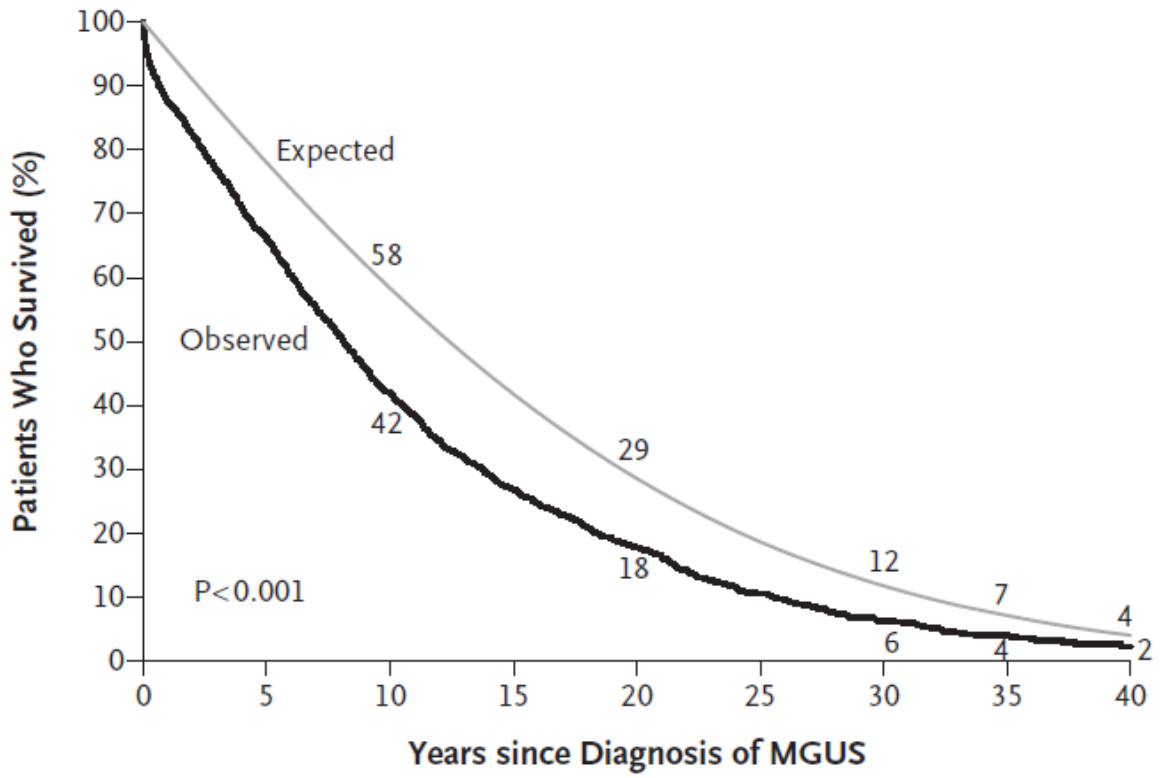


Figure 3. Observed Survival Rate in the Cohort versus the Expected Survival Rate in the Control Population.

The numerical values are the observed rates of survival at 10, 20, 30, 35, and 40 years among the patients in the study and the expected rates in the age- and sex-matched control population.

MGUS: diagnostic différentiel

- amyloïdose AL
- plasmocytome solitaire
- myélome multiple
- lymphomes non HK à cellules B (dont LLC et maladie de Waldenström)
- paraprotéines M secondaires

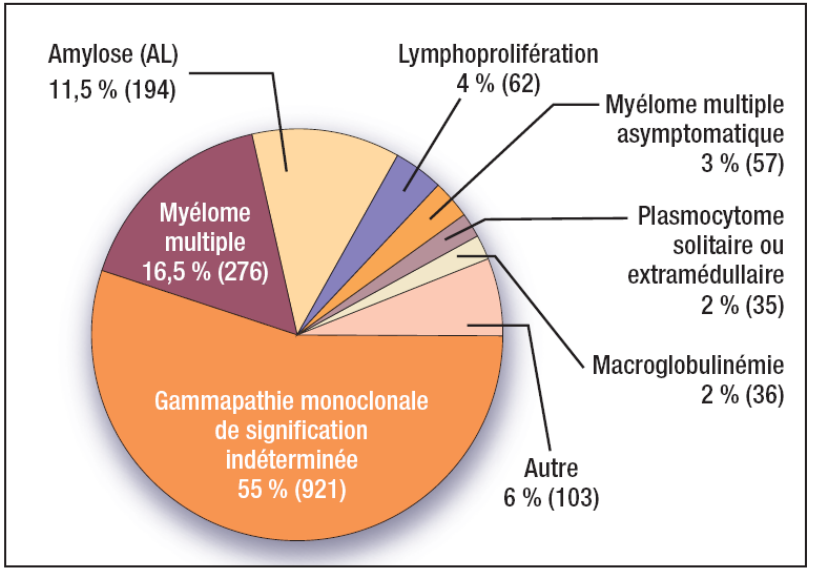


FIGURE 3 **Gammapathies monoclonales. Répartition des causes.**
D'après la *Mayo Clinic Br J Haematol* 2006;134:573-89

ΔΔ

Gammapathies monoclonales secondaires ou associées (pic IgM, IgG, ou IgA)

- ✓ Infections chroniques (biliaires, urinaires), aiguës (mononucléose infectieuse, infections par le cytomégalovirus, par le virus de l'immunodéficience humaine, hépatites, rougeole...)
- ✓ Maladies auto-immunes (polyarthrite rhumatoïde, lupus systémique, périartérite noueuse, syndrome de Gougerot-Sjögren, thyroïdites, IgM anti-myéline...)
- ✓ Hépatopathies cirrhogènes
- ✓ Cancers épithéliaux
- ✓ Néphropathies glomérulaires
- ✓ Certaines affections hématologiques (leucémie myélomonocytaire chronique, quelques myélodysplasies, anémie hémolytique auto-immune)
- ✓ Certains déficits immunitaires constitutionnels
- ✓ Greffe de cellules souches hématopoïétiques
- ✓ Cryoglobulinémie mixte (type II)
- ✓ Maladie de Gaucher

Gammapathies monoclonales à IgM des prolifération lymphoïdes B

- ✓ Maladie de Waldenström
- ✓ Lymphome lymphoplasmocytaire
- ✓ Maladie des agglutinines froides
- ✓ Myélome à IgM (extrêmement rare)
- ✓ Syndrome de Schnitzler

Myélome multiple (IgG, IgA, parfois IgD)

Gammapathies monoclonales associées à une autre hémopathie lymphoïde (IgG ou IgA)

- ✓ Leucémie lymphoïde chronique
- ✓ Lymphomes non hodgkiniens

Gammapathies à chaînes légères ou à chaînes lourdes

- ✓ Amylose primitive AL
- ✓ Maladie à dépôts de chaînes légères d'Ig (anomalies rénales, avec ou sans myélome)
- ✓ Maladie des chaînes lourdes (maladie des chaînes α, μ ou γ, toutes très rares)

Gammapathie monoclonale de signification indéterminée (IgG, IgA, IgM)

- ✓ Diagnostic retenu quand toutes les autres étiologies ont été éliminées

Diagnostic de MGUS

- protéine M : < 30 g/l
- moelle : < 10% plasmocytes clonaux
- pas de désordre prolifératif B
- pas d'atteinte organique ou tissulaire

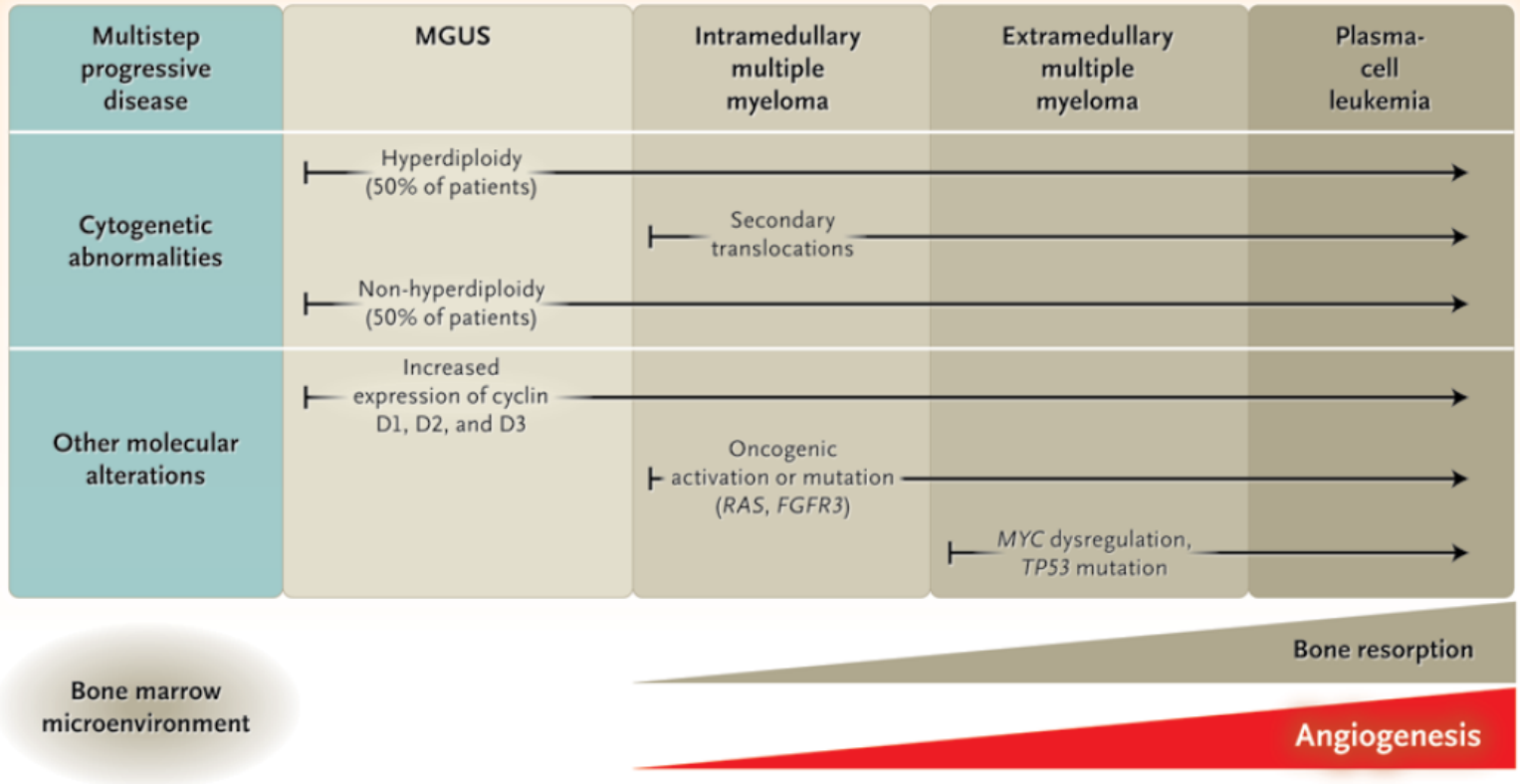


Figure 1. Multistep Pathogenesis of Multiple Myeloma.

Early chromosomal abnormalities (immunoglobulin heavy chain translocations or trisomies) are shared by plasma cells in multiple myeloma and in monoclonal gammopathy of undetermined clinical significance (MGUS). Secondary translocations involving *MYC* (8q24), *MAFB* (20q12), and *IRF4* (6p25) are common in multiple myeloma but quite rare in MGUS. Mutations of *RAS* or *FGFR3, MYC* dysregulation, deletion in p18, or loss of expression or mutation in *TP53* are found only in multiple myeloma and play a key role in determining tumor progression and drug resistance. Also, changes in gene expression, in particular the up-regulation of transcription factors, have been reported in plasma cells from patients with MGUS but not in those from patients with multiple myeloma. Besides molecular alterations of plasma cells, abnormal interactions between plasma cells and bone marrow, as well as aberrant angiogenesis, are hallmarks of disease progression.

N Engl J Med 2011;364:1046-60.

Table 2. Recommended Testing in Patients with Suspected MGUS.

History and physical examination
Hemoglobin concentration
Serum calcium and creatinine concentrations
Protein studies
Total serum protein concentration and serum electrophoresis (serum monoclonal protein concentration)
24-hour urine protein excretion and urine electrophoresis (urine monoclonal protein concentration)
Serum and urine immunofixation (type of monoclonal protein)
Determination of serum free light-chain ratio (kappa and lambda free light chains)*
Examination of bone marrow aspirate†
Skeletal survey†

* This determination is not yet standard procedure but is useful in assessing prognosis.
† This is not recommended if the serum monoclonal protein concentration is below 1.5 g per deciliter.

NOUVEAUX CRITÈRES DIAGNOSTIQUES DU MYÉLOME MULTIPLE (D'APRÈS LA RÉFERENCE 9)		
Définition du myélome multiple		
Plasmocytes médullaires clonaux ≥ 10 % ET 1 ou plus des critères suivants		
Critères CRAB	Hypercalcémie	Calcium sérique > 2,5 mM (> 11 mg/dL) ou > 0,25 mM (> 1 mg/dL) au-dessus de la limite supérieure normale
	Insuffisance rénale	Clairance de la créatinine < 40 mL/min ou créatinine sérique > 177 µM (> 2 mg/dL)
	Anémie	Hémoglobine < 10 g/dL ou > 2 g/dL sous la limite inférieure normale
	Lésions osseuses (*bone lesions*)	Au moins une lésion ostéolytique à la radiographie du squelette, au scanner ou au TEP-scan
OU		
Biomarqueurs de malignité (SLiM)	Plasmocytes médullaires clonaux	≥ 60 %
	Ratio des sFLC	≥ 100 (avec une concentration de la chaîne libre concernée ≥ 100 mg/L)
	Lésions focales à l'IRM	> 1 (diamètre d'au moins 5 mm)

Tableau 1. CRAB : calcium, rein, anémie, *bone* (os) ; IRM : imagerie par résonance magnétique ; sFLC : *serum-free light chains*, chaînes légères sériques ; SLiM : *sixty light chain MRI* (*magnetic resonance imaging*).

Myélome multiple

présence de > 10% plasmatocytes dans la moelle et d'un pic monoclonal dans le sérum ou l'urine (sauf si chaîne légère)

Myélome multiple asymptomatique (indolent – smoldering myeloma)

- Risque de progression de 10% par an
- Attitude : suivi clinique et biologique (EH, créatinémie, calcémie, électrophorèse) : tous les 3 mois

Tableau clinique du myélome multiple

- Hypercalcémie
- Insuffisance rénale
- Anémie
- Tassements vertébraux, atteinte osseuse, compression épidurale
- Infections à répétition
- Hyperviscosité
- Amyloïdose

TABLEAU 3

Classification et pronostic

A. Classification de Durie et Salmon

	Stade I	Stade II	Stade III
Nombre de plasmocytes	$< 0,6 \times 10^{12}/m^2$	$> 0,6 \times 10^{12}/m^2$ $< 1,2 \times 10^{12}/m^2$	$> 1,2 \times 10^{12}/m^2$
Critères de définition	Tous	Ni stade I Ni stade III	Un des suivants
Hémoglobine (g/dL)	> 12		< 10
Calcémie	Normale		> 3 mmol/L
Pic monoclonal (g/L)	IgA < 30, IgG < 50		IgA > 50, IgG > 70
Protéinurie BJ (g/24h)	< 4 g/24 h		> 12 g/24 h
Lésions osseuses	Absente ou isolée		> 3 lésions lytiques

Facteurs de risque

- pic en Ig A ou Ig M
- pic > 1,5 g/dl
- présence de chaînes légères dans le sang (rapport κ/λ)

B. Index pronostique international

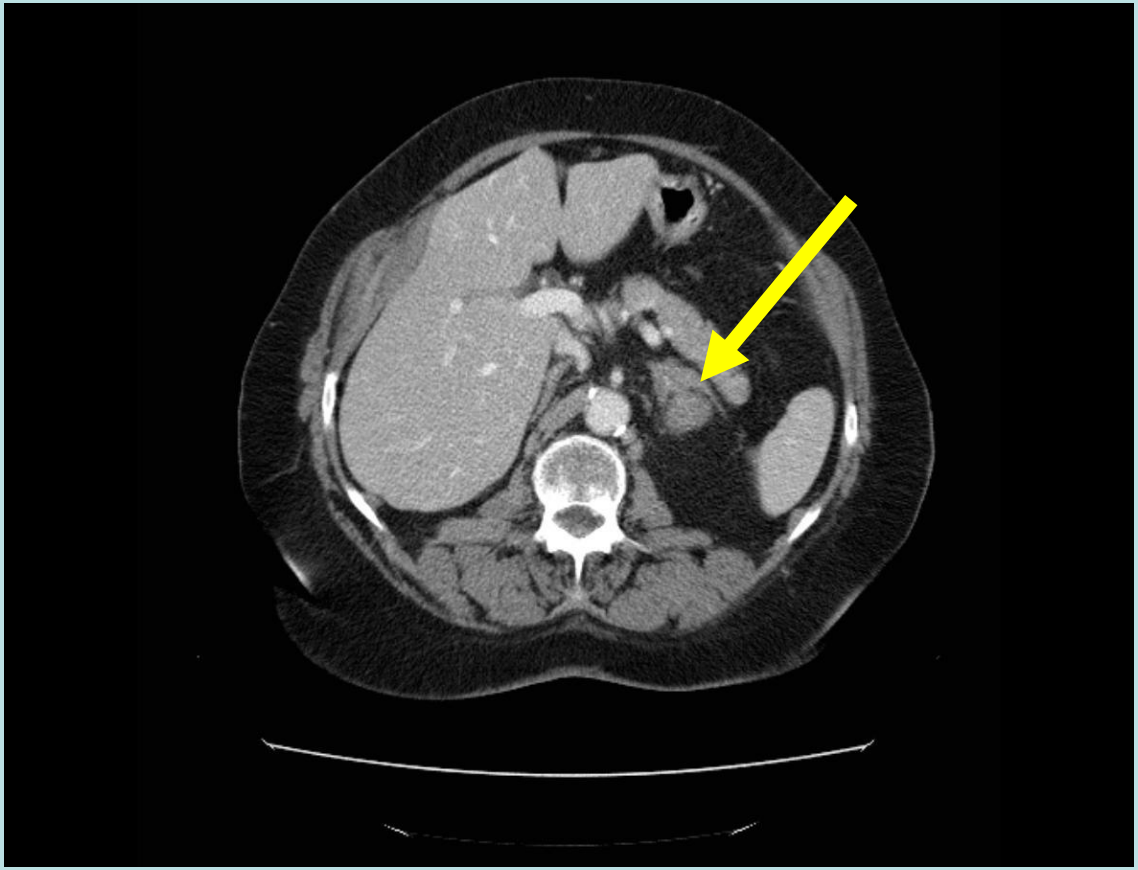
Stade	Critère	Survie médiane (mois)
I	▪ Sérum β_2-microglobuline < 3,5 mg/L ET ▪ Sérum albumine ⩾ 35 g/L	62
II	▪ Sérum albumine < 35 g/L OU ▪ Sérum β_2-microglobuline > 3,5 et < 5,5 mg/L	44
III	▪ Sérum β_2-microglobuline ⩾ 5,5 mg/L*	29

Attitude

suivi selon gravité (contrôle de 1 à 4 x/an)

Incidentalome surrénalien

Cas 3 : découverte d'une masse chez une patiente de 70 ans subissant une TDM dans le contexte d'une BPCO



Définition

- Masse surrénalienne découverte fortuitement lors d'un examen radiologie (échographie TDM, RMN).
- Deux problèmes potentiels:
  - Sécrétion hormonale
  - Malignité
- Envisager TEP

Prévalence

De l'ordre de 4 à 7%, avec une augmentation avec l'âge

Diagnostic différentiel

1. Syndrome de Cushing " subclinique " (hypertension, obésité, ostéoporose, diabète sucré) : 5% (cortisolurie, test de suppression par dexaméthasone).
2. Phéochromocytome asymptomatique : 5% (aspect à la TDM et à la RMN, dosage catécholamines urinaires).
3. Aldostéronisme primaire (adénomes) : 1% (rapport aldostérone plasmatique/activité rénine plasmatique).
4. Tumeurs surrénaliennes produisant des hormones sexuelles œstrogènes ou androgènes (hirsutisme, virilisation) : rares.
5. Hyperplasie bilatérale des surrénales : rare.
6. Métastase : 2,5% (aspect à la TDM, TEP, biopsie)
7. Cancer surrénalien : 5% (aspect à la TDM, TEP, biopsie)
8. Adénome ou tumeur bénigne non sécrétant : si aspect bénin et TEP négative, contrôler l'imagerie de 6 en 6 mois et si progression : chirurgie.

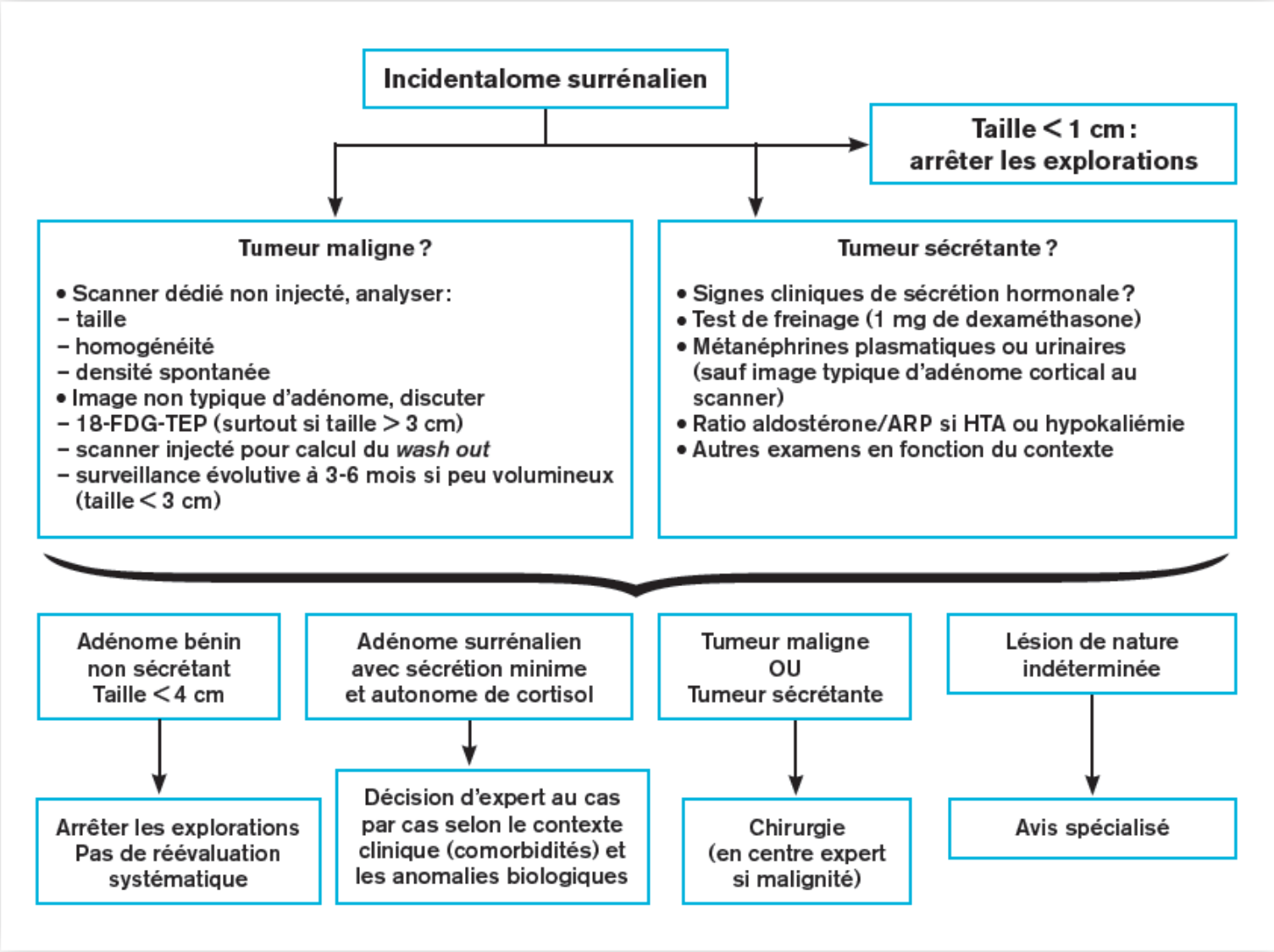
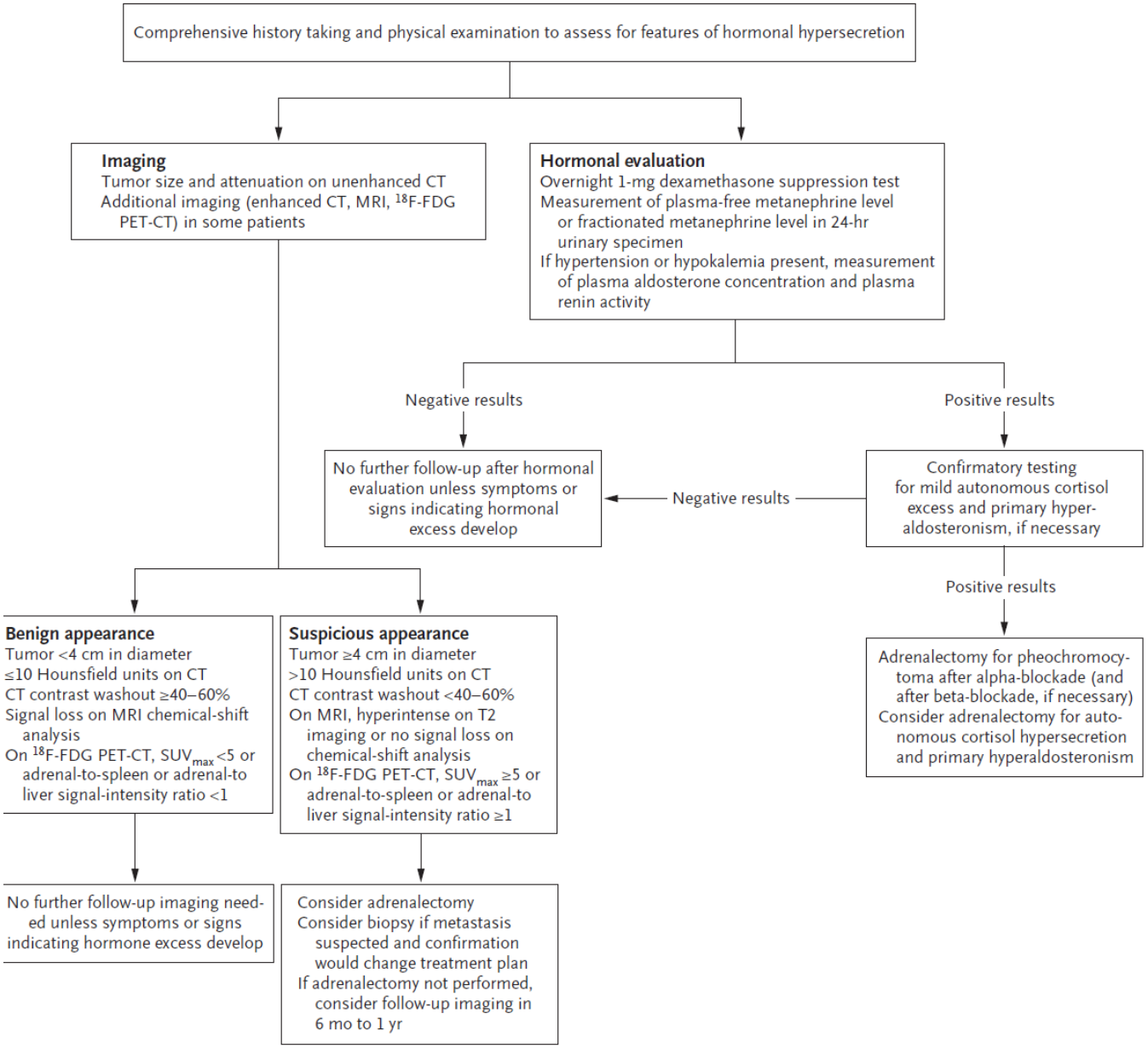


Figure 1. Orientations diagnostique et thérapeutique des incidentalomes surrénaliens. D'après la réf. 1. ARP : activité rénine plasmatique ; HTA : hypertension artérielle ; 18-FDG-TEP : 18-fluorodésoxyglucose-tomographie par émission de positons.



igure 1. Treatment Algorithm for Patients with an Adrenal Incidentaloma.

N Engl J Med 2021;384:1542-51.
DOI: 10.1056/NEJMcp2031112

Table 1. Biochemical Evaluation in Patients with Adrenal Incidentaloma.*

Clinical Diagnosis	Screening Test	Additional or Confirmatory Test	Common Causes of False Positive or False Negative Findings	Special Considerations
Mild autonomous cortisol excess	Overnight dexamethasone (1 mg) suppression test; an abnormal result is a serum cortisol level >1.8 μg per deciliter (50 nmol per liter) with confirmation of serum dexamethasone level (to ensure adherence); a higher serum cortisol cutoff level (e.g., 3–5 μg per deciliter) can be used to reduce the risk of a false positive	Measurement of levels of morning serum corticotropin and cortisol levels, 24-hr urinary cortisol, late-night salivary cortisol, midnight serum cortisol, and DHEAS	False positives may occur in patients receiving medications that accelerate hepatic metabolism of dexamethasone and with nonadherence to dexamethasone	Consider a pseudo-Cushing's syndrome state due to diabetes, obesity, pregnancy, alcoholism, psychiatric disorders, or stress
Pheochromocytoma†	Measurement of levels of plasma-free metanephrines or 24-hr urinary fractionated metanephrines	Not applicable	False positives may occur in patients with stress and illness warranting hospitalization; with medications that increase levels of endogenous catecholamines; with excessive caffeine; and with recreational drug use (e.g., amphetamines)	Biochemical testing may not be necessary if the adrenal mass has CT attenuation of ≤10 Hounsfield units; genetic testing for inherited syndrome should be performed, regardless of family history, if screening test is positive
Primary hyperaldosteronism	Measurement of mid-morning plasma aldosterone concentration and plasma renin activity; a ratio of plasma aldosterone concentration to plasma renin activity >20 confirms diagnosis	If the ratio of plasma aldosterone concentration to plasma renin activity <20, confirmatory testing includes 24-hr urinary aldosterone excretion test with patient receiving high-sodium diet, aldosterone suppression test, and testing with saline infusion while patient is sitting	False positives can be caused by beta-blockers, methyldopa, clonidine, nonsteroidal anti-inflammatory drugs, and oral contraceptives and estrogen; false negatives can be caused by angiotensin-converting–enzyme inhibitors, angiotensin II receptor blockers, and potassium-sparing diuretics (e.g., spironolactone, eplerenone, and amiloride)	If patient is a candidate for adrenalectomy and >35 yr of age, adrenal venous sampling is recommended to confirm lateralization of aldosterone to the side of the adrenal mass (some patients have bilateral aldosterone hypersecretion, or the contralateral adrenal gland may be the source of excess aldosterone and the tumor detected is nonfunctioning)

* Reference ranges for specific assays based on age and sex should be used and may differ from the ranges shown here. DHEAS denotes dehydroepiandrosterone sulfate.

† Additional laboratory tests may include measurement of plasma chromogranin A levels, 24-hour urinary 3-methoxytyramine levels, or both, especially when a malignant pheochromocytoma is suspected because of the presence of potential metastatic disease sites or local invasion.

Table 2. Imaging Features of Adrenal Incidentaloma.*

Feature	Adrenocortical Adenoma	Pheochromocytoma†	Adrenocortical Carcinoma	Metastasis
Size	Usually small, <4 cm in diameter	Variable, frequently large	Large, usually >6 cm in diameter	Variable
Margins and shape	Smooth margins, round or oval	Smooth margins, round or oval	Irregular margins and shape	Irregular margins and shape
Consistency	Homogeneous	Most are heterogeneous (but small ones can be homogeneous)	Heterogeneous	Heterogeneous
Laterality	Usually unilateral but can be bilateral (in 15% of cases)	Usually unilateral but can be bilateral	Usually unilateral	Usually unilateral but can be bilateral
Unenhanced CT attenuation — Hounsfield units	≤10	>10	>10	>10
Contrast-enhanced CT features				
Attenuation	Low	High	High	High
Vascularity	Low	High	High	Usually high
Washout‡	Fast	Slow	Slow	Slow
MRI features	Isointense in relation to liver on T2-weighted image; signal drop on chemical-shift imaging	Hyperintense in relation to liver on T2-weighted image; no signal drop on chemical-shift imaging	Markedly hyperintense in relation to liver on T2-weighted image; no signal drop on chemical-shift imaging	Hyperintense in relation to liver on T2-weighted image; no signal drop on chemical-shift imaging
^{18}F-FDG PET-CT features				
Avidity	Not avid	Avid	Avid	Avid
SUV_{max}	<5	Usually ≥5§	Usually ≥5§	Usually ≥5§
Adrenal-to-spleen or adrenal-to liver signal-intensity ratio¶	<1.0	≥1.0–1.5	≥1.0–1.5	>≥1.0–1.5 but may vary based on primary origin of cancer
Necrosis, calcification, and hemorrhage	Uncommon	Hemorrhagic, necrotic, and cystic areas more common in larger tumors	Necrosis, calcification, and hemorrhage are common	Hemorrhagic, necrotic, and cystic areas more common in larger tumors

* Myelolipoma and adrenal cysts have typical imaging features on CT and or magnetic resonance imaging (MRI). ^{18}F-FDG PET-CT denotes positron-emission tomography (PET)–CT with ^{18}F-fluorodeoxyglucose, and SUV_{max} maximum standardized uptake value.

† The presence of metastasis is the only way to determine whether a pheochromocytoma is malignant. Metastatic pheochromocytoma is associated with larger tumors (>6 cm in diameter) and irregular margins.

‡ Washout of contrast medium has been measured at various times (60 to 90 seconds [early] and 10 to 15 minutes [late]) with both relative and absolute values. Absolute washout is defined as the attenuation value in Hounsfield units on early enhanced CT minus Hounsfield units on delayed CT, divided by Hounsfield units on early enhanced CT minus Hounsfield units on unenhanced CT, multiplied by 100%, and relative washout is defined as Hounsfield units on early enhanced CT minus Hounsfield units on delayed CT, divided by Hounsfield units on enhanced CT, multiplied by 100%. Absolute washout values greater than 60% and relative washout values greater than 40% suggest an adenoma.[34]

§ Some studies have used an SUV_{max} cutoff value that is less than 5.

¶ The adrenal-to-spleen signal-intensity ratio (i.e., the signal intensity of the adrenal mass divided by the signal intensity of the spleen) and the adrenal-to-liver signal-intensity ratio (i.e., the signal intensity of the adrenal mass divided by the signal intensity of the liver) are based on meta-analyses and prospective studies.[34] Some studies have used adrenal-to-spleen or adrenal-to-liver SUV_{max} ratios.

Incidentalome génétique

CHEST

Commentary

AHEAD OF THE CURVE

Grappling With Genomic Incidental Findings in the Clinical Realm

Sara Chandros Hull, PhD; and Benjamin E. Berkman, JD, MPH

We have learned a remarkable amount in recent decades about genomics and its potential contributions to human health and medical practice. However, genomic sequencing technology, which is starting to become incorporated into clinical care, also raises ethical challenges. In particular, there has been significant debate about the appropriate management of genomic incidental findings (GIFs), which we define as pathogenic or likely pathogenic test results that are not apparently relevant to the diagnostic indications for which the tests were ordered. Although there is an emerging consensus that clinicians will have at least some obligation to disclose GIFs to patients, the scope of that obligation is unclear. This commentary identifies nuanced issues that clinicians will likely face in the foreseeable future regarding their emerging obligations to disclose clinically actionable GIFs. Will clinicians be expected to look actively for GIFs? Should GIFs for adult-onset disorders be disclosed to children? What obligations will clinicians have to disclose GIFs to family members of deceased patients? What role should informed consent play? There is value to exploring the range of views on these questions at this time, before genomic sequencing has fully matured as a technology, so that clinicians can anticipate how they will respond to the discovery of GIFs once sequencing becomes a more routine part of clinical care. Genomics is ultimately going to play an important role in the practice of pulmonary medicine, and it is important for pulmonologists and other subspecialists to be well informed about what to expect.

CHEST 2014; 145(2):226–230

Abbreviations: ACMG = American College of Medical Genetics; GIF = genomic incidental finding

Incidentalomas in Genomics and Radiology

Benjamin D. Solomon, M.D.

When a lesion is found incidentally or secondarily on radiology, steps are frequently available for relatively efficiently reaching a definitive answer. In genomics, by contrast, it is often more difficult to determine in a timely or satisfying manner whether a genetic variant is pathogenic.

DOI: 10.1056/NEJMp1310471

médecine/sciences 2014 ; 30 : 227-8

Éditorial

Grandes manœuvres autour des profils génétiques en libre accès

Bertrand Jordan

ÉDITORIAL

- Quelle est la valeur prédictive des informations tirées de l'analyse de notre génome, et pourquoi sa perception par le grand public est-elle aussi déformée ?
- Une entreprise (23andMe) a-t-elle le droit de commercialiser des informations de cette nature « en direct », au risque que celles-ci soient mal interprétées en l'absence de tout contrôle médical ?
- D'un autre côté, la règlementation d'un tel processus ne constitue-t-elle pas une atteinte à la liberté individuelle ?
- Existe-t-il un risque que de tels travaux, monopolisés par une firme qui a réussi à éliminer ses concurrents, débouchent sur l'appropriation d'associations génétiques médicalement importantes ?