AGeMIG – HUG/Centre AHBP
Formation continue conjointe_09.12.2021

Cancer du pancréas : consultation d'oncogénétique ?

Pr Pierre CHAPPUIS

Service de médecine génétique
Service d'oncologie

UNIVERSITÉ DE GENÈVE

HUG Hôpitaux Universitaires Genève

CP1

Carcinome du pancréas

	Nouveaux cas/an	Décès/an
Hommes	760	643
Femmes	742	662
Total	**1’502**	**1’305**

[2013-2017; www.ocnec.ch]

- **Risque cumulatif : ~1.2 %**
- **Age médian : 71 ans**
  - 4 % cas < 50 ans
  - 61 % cas > 70 ans

	Nouveaux cas/an	Décès/an
Hommes	46	39
Femmes	43	38
Total	**89**	**77**

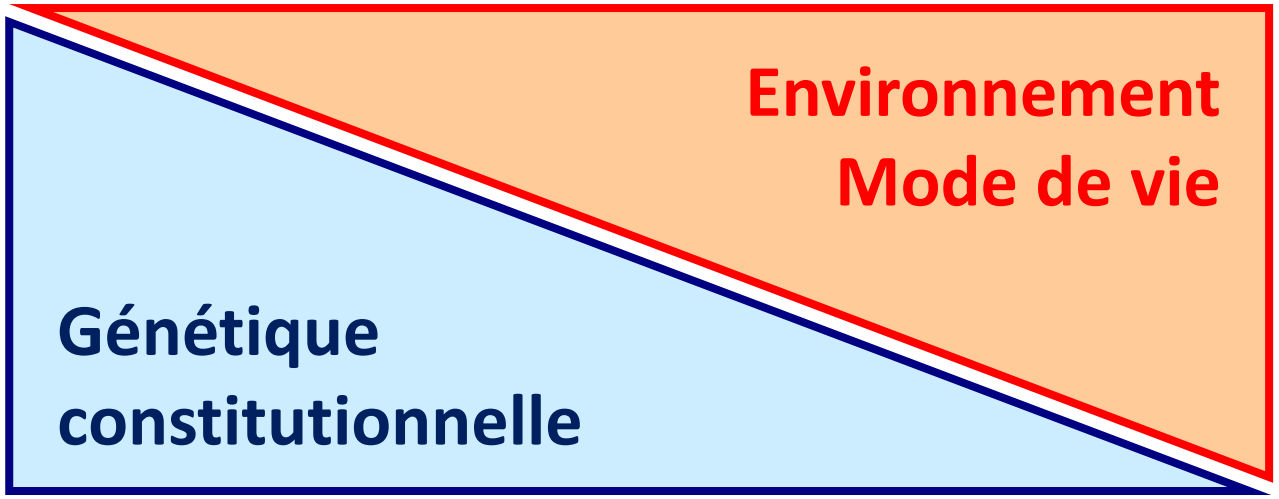
[2014-2018; RGT]

Diapositive 2

CP1 CHAPPUIS Pierre; 08.12.2021

Carcinomes du pancréas
Facteurs de risque

C



Carcinomes du pancréas
Facteurs de risque

Definite risk factors	Possible risk factors	Unclear risk*
Increasing age	Poor diet: high intake of fat, low intake of fresh fruit and vegetables	Diabetes mellitus type 1
Tobacco smoking	Occupational exposure (cadmium, chromium, radon)	
Chronic pancreatitis	Diabetes mellitus type 2	
Hereditary pancreatitis		

*Causal association demonstrated in small cohort and case–control studies; further proof needed.

[R. Lochan et al. Br JSurg 2008]

Susceptibilité génétique : 5-15 %

Antécédents familiaux → risque familial/héréditaire

Carcinomes du pancréas
Agrégations familiales (non syndromiques)

Table 1. Familial Aggregation Studies of Pancreatic Cancer

Study Design, Location	Study Population	Result[a]	Source, y
Case-control, population-based, Quebec, Canada	179 cases 179 controls	OR = 13-fold ($P < .001$)[b]	Ghadirian et al,[9] 1991
Case-control, hospital-based, Northern Italy	362 cases 1408 controls	OR = 2.8 (1.3–6.3)[c]	Fernandez et al,[91] 1994
Case-control, hospital-based, Louisiana, United States	363 cases 1234 controls	OR = 5.25 (2.08–13.21)[c]	Falk et al,[92] 1988
Case-control, population-based, United States	484 cases 2099 controls	OR = 3.2 (1.8–5.6)	Silverman,[10] 2001
Case-control, population-based, Southeastern Michigan, United States	247 cases 420 controls	RR = 2.49 (1.32–4.69)[d]	Schenk et al,[93] 2001
Case-control, hospital-based, Texas, United States	808 cases 808 matched controls	OR = 2.7 (1.7–4.3)	Hassan et al,[94] 2007
Nested case-control, Japan	200 cases 2000 matched controls	OR = 2.09 (1.01–4.33)	Inoue et al,[95] 2003
Cohort, United States	3751 cases among 1 102 308 individuals, 14 y of follow-up	RR = 1.5 (1.1–2.1)[e]	Coughlin et al,[11] 2000
Cohort, Sweden	21 000 cases among 10.2 million individuals	RR = 1.73 (1.13–2.54)	Hemminki and Li,[96] 2003

Abbreviation: CI, confidence interval; OR, odds ratio; RR, relative risk.

[a] Results are calculated as -fold increase for OR (*P* value) for data by Ghadirian et al[9] and as either OR or RR (95% CI) for all other data.
[b] Age, sex, and language (French) matched.
[c] Adjusted for tobacco use, dietary factors, and history of diabetes and pancreatitis, crude OR of 3.0.
[d] Adjusted for age, sex, ethnicity, ever smoking, proband ever smoking, diabetes, and age of proband.
[e] Adjusted for dietary factors, body mass index, gallstone history, cholecystectomy history, diabetes, age, race, years of education (age-adjusted rate was equivalent).

[Shi & al. Arch Pathol Lab Med 2009]

Définition des cancers du pancréas familiaux

- ≥ 2 parents en lien du 1er degré *ou*
- ≥ 3 membres d'une même branche familiale

Carcinomes du pancréas
Syndromes génétiques

Table 1. Risk for Pancreatic Cancer Related to Genetic Mutation

Genes	Common name	Risk of pancreatic cancer
STK11/LKB1	Peutz–Jeghers syndrome	RR, 132 (95% CI, 44–261)
PRSS1	Hereditary pancreatitis	SIR, 53 (95% CI, 23–105)
CDKN2A	Familial atypical multiple mole/melanoma syndrome	RR, 13–39
MLH1, MSH2, MSH6	Lynch syndrome	RR, 8.6–11
TP53	Li-Fraumeni syndrome	RR, 7.3 (95% CI, 2–19)
ATM	NA	RR, 3.92 (95% CI, 0.44–14.2)
BRCA1	Hereditary breast and ovarian cancer	RR, 2.26 (95% CI, 1.26–4.06)
BRCA2, PALB2		RR, 3.5–6.2 (95% CI 1.87–6.58)
Familial pancreas cancer in 1 or 2 first-degree relatives	Familial pancreas cancer	RR, 4–9.3

[Aslanian et al. Gastroenterol 2020]

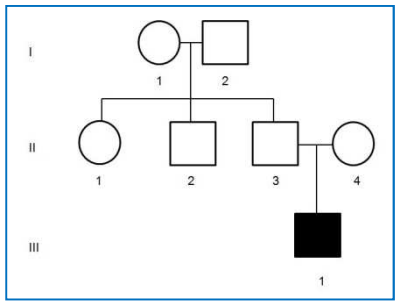
- Transmission mendélienne (AD)
- Pénétrance variable (cf. RR)

The Family History — More Important Than Ever

Alan E. Guttmacher, M.D., Francis S. Collins, M.D., Ph.D., and Richard H. Carmona, M.D., M.P.H.

The NEW ENGLAND JOURNAL of MEDICINE
NOVEMBER 25, 2004

- Branches mat. et pat.
- ≥ 3 générations
- Types de cancer
- Ages au diagnostic
- Ethnicité
- Liens de parenté



Antécédents familiaux ou personnels	Gènes de prédisposition
Cancer du sein	*BRCA2, BRCA1, PALB2, ATM*
Cancer de l'ovaire	*BRCA2, BRCA1, BRCA2, ATM*
Cancer colorectal	*MLH1, MSH2, MSH6, PMS2* (syndrome de Lynch)
Cancer de l'utérus (endomètre)	*MLH1, MSH2, MSH6, PMS2* (syndrome de Lynch)
Mélanome	*CDKN2A* (syndrome FAMMM)
Polypose hamartomateuse, cancers dig., lésions pigmentées, cancer du sein, …	*STK11* (synd. de Peutz-Jeghers)
Cancer du pancréas (agrégations fam.)	*BRCA2, BRCA1, PALB2, CDKN2A, ATM, MLH1, MSH2, MSH6, PMS2, STK11, TP53*
Pancréatites	*PRSS1, SPINK1*

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

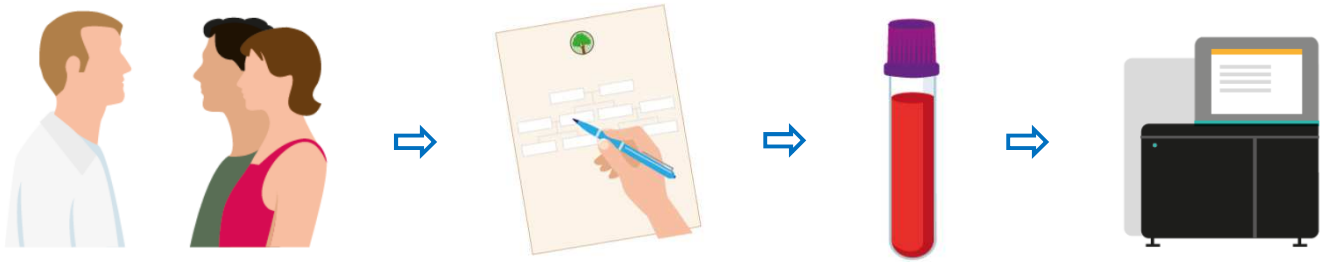
Review article: Medical guidelines | Published 13 September 2021 | doi:10.4414/SMW.2021.w30038
Cite this as: Swiss Med Wkly. 2021;151:w30038

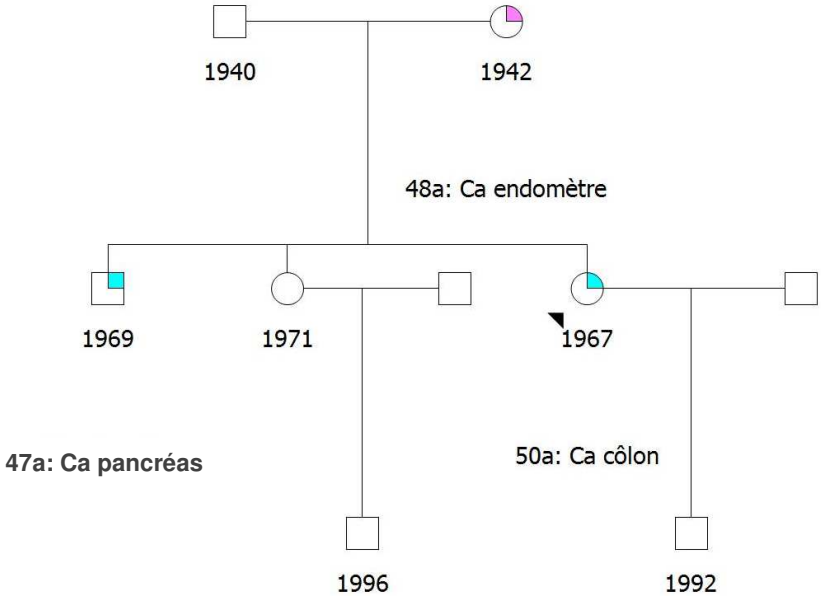
Update Swiss guideline for counselling and testing for predisposition to breast, ovarian, pancreatic and prostate cancer

Susanna Stoll[a], Sheila Unger[b], Silvia Azzarello-Burri[c*], Pierre Chappuis[d*], Rossella Graffeo[e*], Gabriella Pichert[f*], Benno Röthlisberger[g*], Francois Taban [h*], Salome Riniker [i], on behalf of the Swiss Group for Clinical Cancer Research (SAKK) Network for Cancer Predisposition Testing and Counselling (CPTC)

VIII. Pancreatic cancer	Exocrine pancreatic cancer at any age (first step: tumour profiling)	
	Unaffected individuals with	familial pancreatic cancer (2 first-degree relatives with pancreatic cancer)
		≥3 individuals with pancreatic cancer (same side of the family)[8]

Consultation d'oncogénétique





- validation des diagnostics
- **consensus interne**

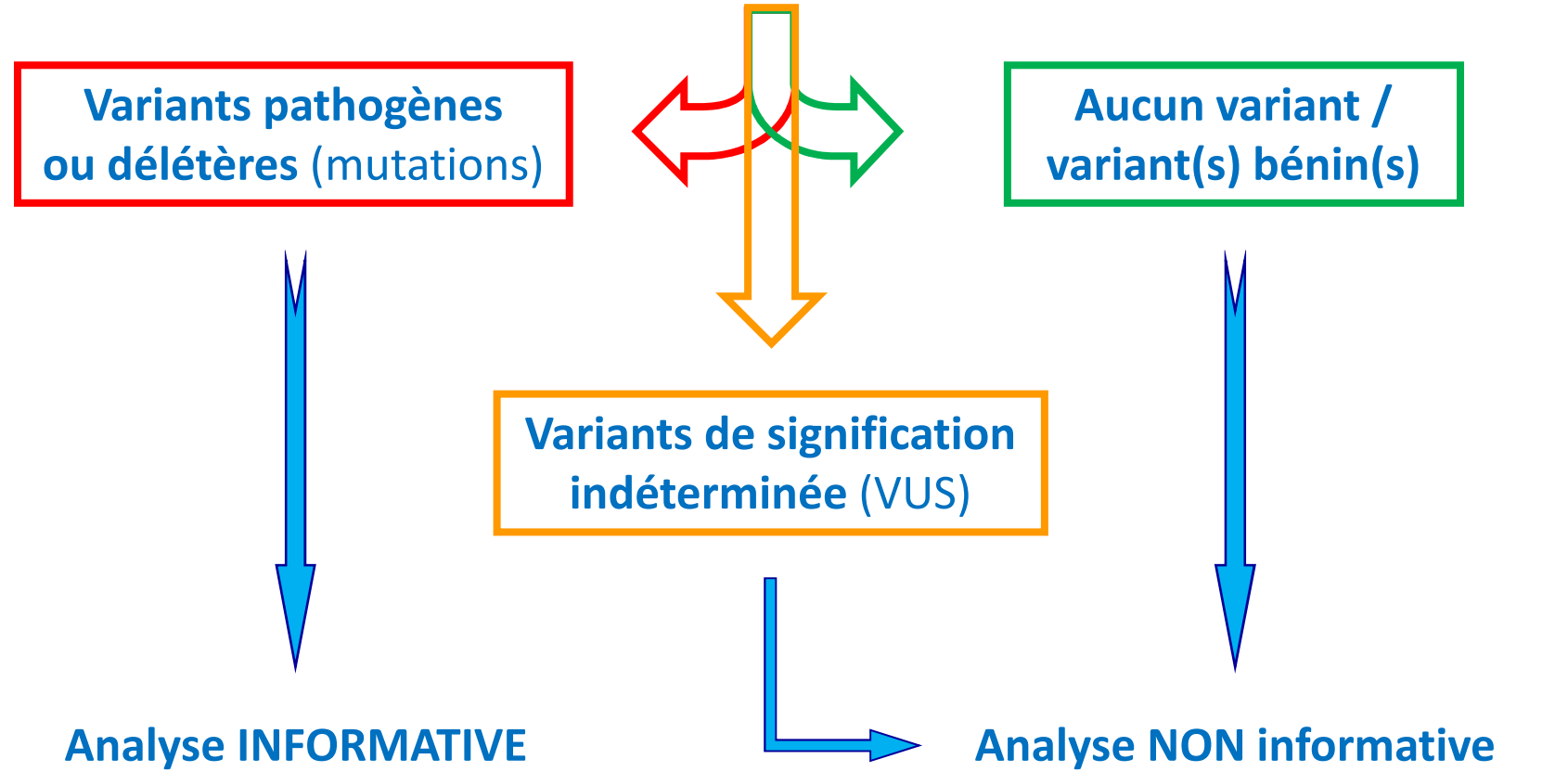
Gènes de prédisposition au cancer

Résultats du séquençage

Variants pathogènes ou délétères (mutations)

Aucun variant / variant(s) bénin(s)

Variants de signification indéterminée (VUS)



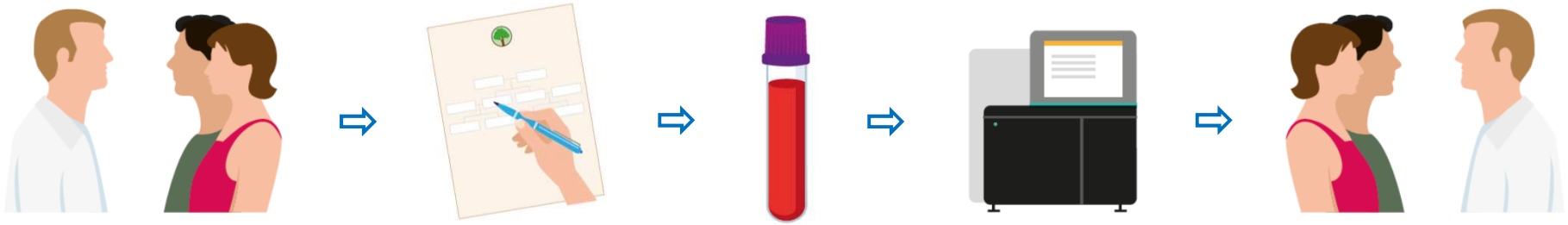
Analyse INFORMATIVE

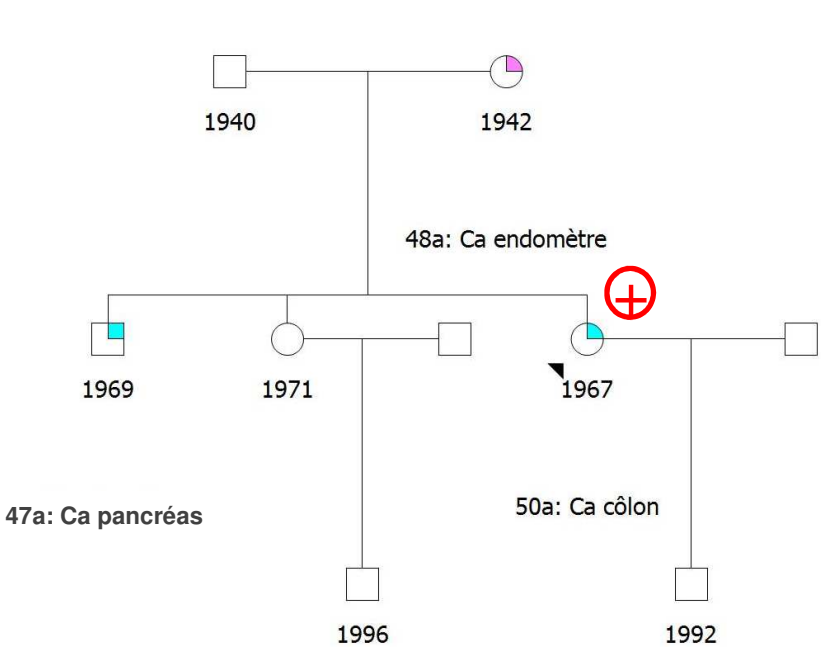
- Evaluation du risque oncologique basée sur le résultat ➔ programme de surveillance et de prévention selon des recommandations internationales
- Possibilité de proposer une analyse ciblée à la parenté

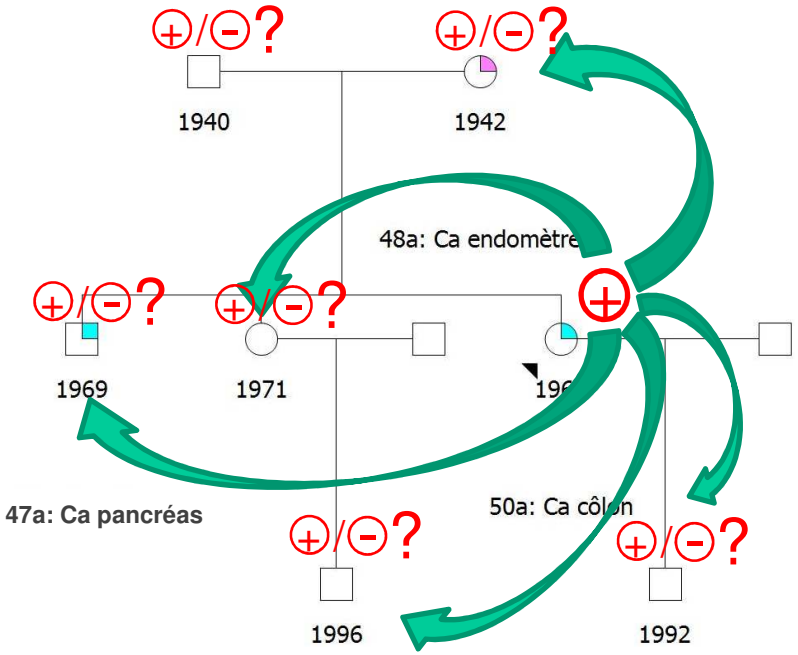
Analyse NON informative

- Evaluation du risque oncologique basée sur l'anamnèse familiale et personnelle
- Pas d'analyse ciblée chez les apparentés

Consultation d'oncogénétique







Mesures de surveillance/prévention adaptées au résultat

Cancer du pancréas : dépistage

International Cancer of the Pancreas Screening Consortium

Table 3 Summary of the main recommendations of the 2019 International Cancer of the Pancreas Surveillance (CAPS) Consortium

Who?	
► All patients with Peutz-Jeghers syndrome (carriers of a germline *LKB1/STK11* gene mutation) ► All carriers of a germline *CDKN2A* mutation ► Carriers of a germline *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *MLH1*, *MSH2*, or *MSH6* gene mutation with at least one affected first-degree blood relative ► Individuals who have at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer (familial pancreatic cancer kindred)	
When (at what age)?	
► Age to initiate surveillance depends on an individual's gene mutation status and family history	
Familial pancreatic cancer kindred (without a known germline mutation)	Start at age 50 or 55* or 10 years younger than the youngest affected blood relative
Mutation carriers: For *CDKN2A*†, Peutz-Jegher syndrome, start at age 40; *BRCA2*,*ATM*, *PALB2 BRCA1*, *MLH1/MSH2* start at age 45 or 50 or 10 years younger than youngest affected blood relative	

[Goggins et al. Gut 2020;
Aslanian et al. Gastroenterol 2020]

- Les modalités de dépistage sont à définir en centre expert et doivent reposer sur des examens non irradiants : **échoendoscopie et IRM**.
- La correction des autres facteurs de risque est recommandée (tabagisme, obésité)**.**

[Thésaurus National de Cancérologie Digestive, 2021]

CONCLUSION

- L'anamnèse familiale est une information clinique essentielle
- 5-15 % des cancers du pancréas sont liés à des prédispositions génétiques (pas toujours identifiables)
- Les principaux gènes de prédisposition au cancer du pancréas : *STK11*, *PRSS1, CDKN2A*, *BRCA2*, *ATM*, *PALB2*, *MLH1*, *MSH2*
- Un conseil génétique encadre toute analyse visant à identifier des porteurs/non-porteurs de prédispositions au cancer
- Quid de l'impact des mesures de surveillance du pancréas ?
- Prise en charge pluridisciplinaire complexe des personnes portant des prédisposition au cancer

Pour nous joindre

Unité d'oncogénétique

Service d'oncologie_HUG

☎ : 022 372 98 53 (secrétariat)

Dre Fulvia BRUGNOLETTI : fulvia.brugnoletti@hcuge.ch

Pr Pierre CHAPPUIS : pierre.chappuis@hcuge.ch