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SYMPTOMATIC CONTROL OF FUNCTIONING PANCREATIC NET

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BACKGROUND PANCREATIC NET

- Pancreatic neuroendocrine tumours (panNETs) account for approx. 1-2% of all pancreatic tumours
- PanNETS can be divided into 2 groups based on the functional activity of the tumour:
  - **Functioning pancreatic NET**
  - **Non-functioning pancreatic NET**
- Around 60-90% of panNETs are non-functioning and often only diagnosed as a result of an incidental finding for a different indication
- Functioning panNETs secrete active hormones, most commonly insulin or gastrin, leading to symptoms even when the tumour is small
- **Functioning panNET, include:**
  - **Insulinoma –** secrete insulin. Signs/symptoms: hypoglycaemia
  - **Glucagonoma –** secrete glucagon. Signs/symptoms: diabetes mellitus, necrolytic migratory erythema, deep vein thrombosis and depression
  - **Gastrinoma** (Zollinger-Ellison Syndrome) **–** secrete gastrin. Signs/symptoms: gastroesophageal reflux, peptic ulcers, diarrhoea
  - **VIPoma –** produce vasoactive intestinal peptide. Signs/symptoms: watery diarrhoea, achlorhydria, and hypokalaemia
- **Rare functioning panNET:** somatostatinoma, cholecystokinin-producing tumours (CCKoma), ghrelinoma

NET, neuroendocrine tumour

Falconi M, et al. Neuroendocrinology. 2016;103:153-71; Hopper A, et al. Frontline Gastroenterol. 2019;10:269-74; Bartolini I, et al. Gastroenterol Res Pract 2018: doi.org/10.1155/2018/9647247; Rehfeld J, et al. Scand J Gastroenterol 2016; 51: 1172-1178; Tsolakis A, et al. J Clin Endocrinol Metab 2004, 89: 3739–3744; Zandee W, et al. https://www.ncbi.nlm.nih.gov/books/NBK279041/

DIAGNOSIS OF FUNCTIONING panNET

- **Clinical syndrome in combination with inappropriately increased hormone**

Not diagnostic:

- Immunohistochemical staining of hormones on tumour specimen
- Screening for elevated hormones without clinical syndrome

panNET, pancreatic neuroendocrine tumour

Falconi M, et al. Neuroendocrinology 2012; 95; 120-134; Falconi M, et al. Neuroendocrinology. 2016;103:153-71; Hofland J, et al. Nat Rev Endocrinol. 2018;14:656-69

DIAGNOSIS – FUNCTIONING panNET

INSULINOMA

Either spontaneous or during 72-hour fast:

- Blood glucose levels ≤2.1 mmol/l
- insulin levels >18 pmol/l
- C-peptide levels ≥0.2 nmol/l
- proinsulin levels ≥5 pmol/l;
- β-hydroxybutyrate levels ≤2.7 mmol/l
- Negative screening of OHA (eg.no sulfonylurea metabolites) in the plasma and/or urine

VIPoma

- VIP levels 1-3 × upper limit of normal (ULN) considered inconclusive: re-test
- ***Diagnostic for VIPoma:*** plasma VIP levels >3 × ULN are considered indicative of a VIP-producing tumour

GLUCAGONOMA

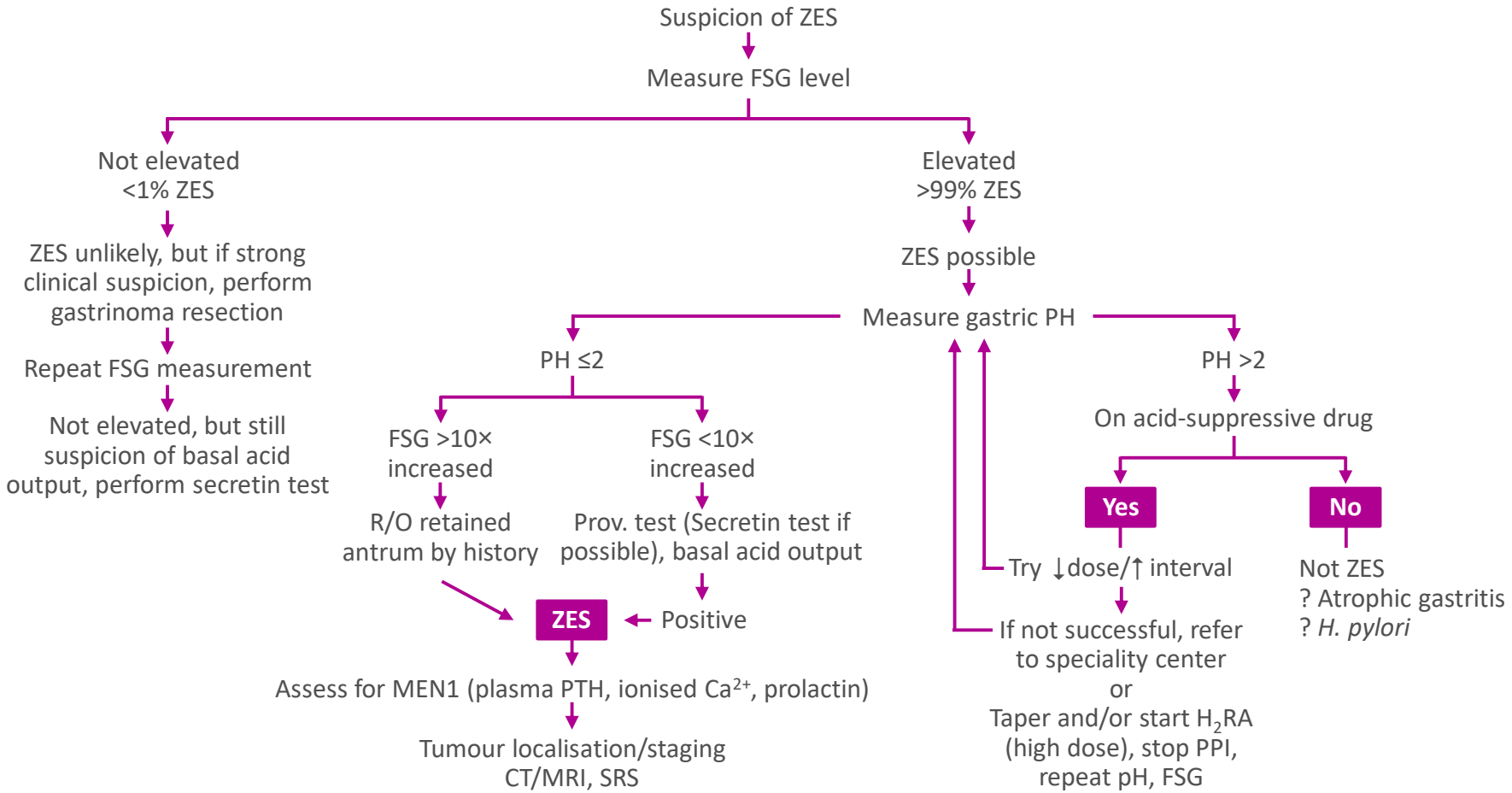
- Fasting plasma glucagon >500 pg/ml (reference range, 70-160 pg/ml) is diagnostic for glucagonoma

panNET, pancreatic neuroendocrine tumour; OHA, oral hypoglycaemic agents; ULN, upper limit of normal; VIP, vasoactive intestinal peptide

Falconi M, et al. Neuroendocrinology. 2016;103:153-71; Hofland J, et al. Nat Rev Endocrinol. 2018;14:656-69; Zandee W, et al. https://www.ncbi.nlm.nih.gov/books/NBK279041/; de Herder W, et al. https://www.ncbi.nlm.nih.gov/books/NBK278981/Accessed 27-Nov-20; Bloom, SR. Am J Dig Dis 1978;23:373-6; Cryer P, et al. JCEM 2009; 94: 709-728

DIAGNOSIS OF GASTRINOMA

ZOLLINGER-ELLISON SYNDROME



BAO, basal acid output; CT, computerized tomography; FSG, fasting serum gastrin; H2RA, H2 receptor antagonist; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; PPI, proton pump inhibitor; PTH, parathyroid hormone; R/O, rule out; SRS, stereotactic radiosurgery; ZES, Zollinger-Ellison Syndrome

Falconi M, et al. Neuroendocrinology. 2016;103:153-71

TREATMENT OPTIONS

- **If radical resection is feasible:** curative surgery is recommended
- **Metastatic/non-resectable panNET:**
  - Combination of anti-proliferative and anti-hormone therapies
- **Symptom control is essential:**
  - Signs and symptoms of a functional pancreatic NET depend on the type of hormone being made
  - Excessive secretion of hormones can impair a patient's quality of life and prognosis
  - Symptomatic control is required to safely perform surgery or treat with systemic therapy

NET, neuroendocrine tumour; panNET, pancreatic neuroendocrine tumour

Pavel M, et al. Neuroendocrinology. 2016;103:172-85; Falconi M, et al. Neuroendocrinology. 2016;103:153-71;
Akirov A, et al. Cancers 2019; 11; 828; doi:10.3390/cancers11060828

FUNCTIONING panNET: FIRST-LINE THERAPY

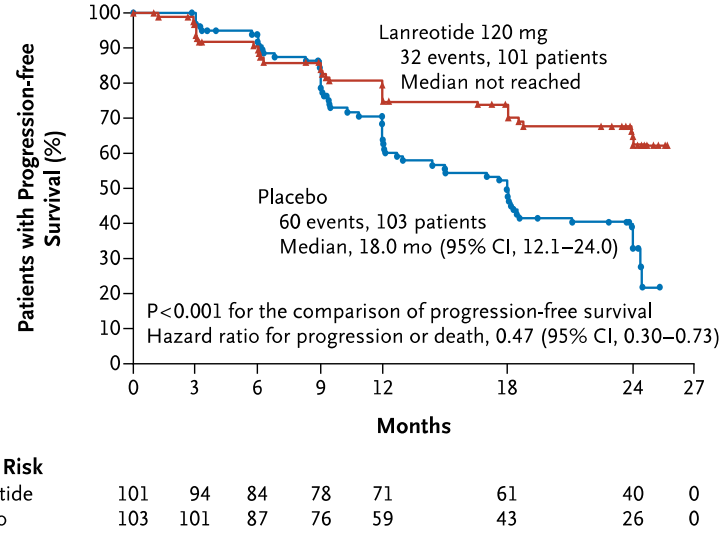
SOMATOSTATIN ANALOGUES

- Antiproliferative effect in panNET[1]
  - lanreotide (120 mg every 4 weeks) significantly prolonged PFS compared with placebo [HR 0.47*, (95% CI 0.30-0.73)]
- Low toxicity[1]
- SSAs reduces hormone secretion in approx. 50-70% of patients[2]
- Consider dose escalation, if standard dosing proves ineffective
  - An increased dose frequency of lanreotide (120 mg every 14 days) demonstrated favourable PFS and DCR data[3]

Insulinoma: some SSAs also decreases glucagon secretion[4,6]

- In a minority of insulinoma patients SSA increases hypoglycemia[5]
  - initiate treatment with short-acting octreotide in a clinical setting[6]

CLARINET TRIAL: PFS



*HR for progression or death

CI, confidence interval; DCR, disease control rate; HR, hazard ratio; panNET, pancreatic neuroendocrine tumour; PFS, progression free survival; SSA, somatostatin analog; sc, subcutaneous

1. Caplin M, et al. N Engl J Med. 2014;371:224-33; 2. Grozinsky-Glasberg S, et al. Endocr Relat Cancer. 2008;15:701-20; 3. Pavel M, et al. ESMO 2020. Abstract #1162MO. Mini oral presentation; 4. Lins P-E, et al. Metabolism 1980; 29; 728-731; 5. Kulke M, et al. Pancreas 2010;39:735-52; 6. Akirov A, et al. Cancers 2019; 11; 828; doi:10.3390/cancers11060828

INSULINOMA: SYMPTOMATIC TREATMENT

MANAGING HYPOGLYCAEMIA

Dietary management

- Frequent meals, slowly absorbable carbohydrates

- **Diazoxide** inhibits the release of insulin by β cells
- Stimulates gluconeogenesis
- Side effects: sodium retention (treated with thiazide-diuretic), hirsutism

de Herder W, et al. https://www.ncbi.nlm.nih.gov/books/NBK278981/Accessed 27-Nov-20; https://www.drugs.com/sfx/diazoxide-side-effects.html. Accessed 08-Dec-2020

OTHER FUNCTIONAL panNET: SYMPTOMATIC TREATMENT

Gastrinoma – gastric acid hypersecretion:

- Protonpump inhibitors

VIPoma

- Replacement of fluid and electrolyte losses

Glucagonoma

- Correct malnutrition and hyperglycaemia
- Consider low-molecular weight heparin to prevent venous thrombosis

panNET, pancreatic neuroendocrine tumour

Falconi M, et al. Neuroendocrinology. 2016;103:153-71; Hopper A, et al. Frontline Gastroenterology. 2019;10:269-74; Vinik, A. https://www.ncbi.nlm.nih.gov/books/NBK278960/. Accessed 27-Nov-20; Zandee W, et al. https://www.ncbi.nlm.nih.gov/books/NBK279041/. Accessed 27-Nov-20

FUNCTIONING panNET: SECOND-LINE THERAPY

If first-line treatment with SSAs do not provide adequate control of symptoms or after radiological progression, then consider *(depending on local availability and patient characteristics)*:

- **PRRT** with Lu^{177}-DOTATATE
- **Targeted therapies** – everolimus and sunitinib
- **Palliative debulking surgery** – in the presence of unresectable liver metastases
- **Liver-directed therapies**

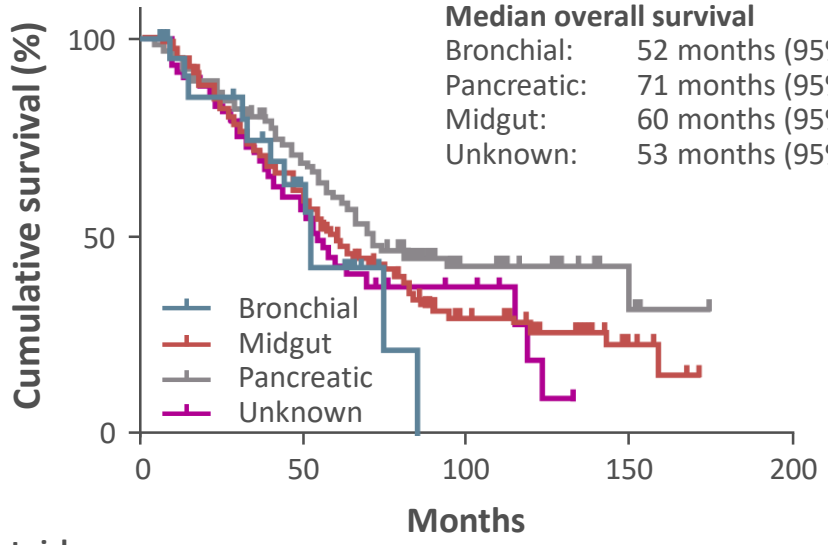
Lu^{177}, lutetium 177; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analog

Falconi M, et al. Neuroendocrinology. 2016;103:153-71; Hopper A, et al. Frontline Gastroenterology. 2019;10:269-74; Andreasi V, et al. Curr Treat Options in Oncol 2020; 21: DOI 10.1007/s11864-020-00736-w

PROSPECTIVE, SINGLE-ARM TRIAL

- Approx. 1,200 patients treated with PRRT [^{177}Lu-DOTATATE] since the year 2000
- Subgroup analysis n=443 (panNET=133)
  - Treated with a cumulative dose of ≥600 mCi (22.2 GBq) ^{177}Lu-DOTATATE before 2013
- panNET results
  - Objective response: 55%
  - median PFS: 30 months
- Long-term toxicity: MDS: 1.5% / AML: 0.7%

MEDIAN OS BY LOCATION OF PRIMARY TUMOUR



No. at risk				
Bronchial	23	10	0	0
Midgut	181	92	28	7
Pancreatic	133	71	17	4
Unknown	82	31	7	0

AML, acute myeloid leukaemia; CI, confidence interval; Lu177, lutetium 177; MDS, myelodysplastic syndromes; OS, overall survival; panNET, pancreatic neuroendocrine tumour; PFS, progression free survival; PRRT, peptide receptor radionuclide therapy

Brabander T, et al. Clin Can Res. 2017;23:4617-24

PRRT: LU^{177}-DOTATATE FOR FUNCTIONING panNET

Functioning panNET can safely be treated with PRRT, however preventive therapy for hormone symptoms is required.

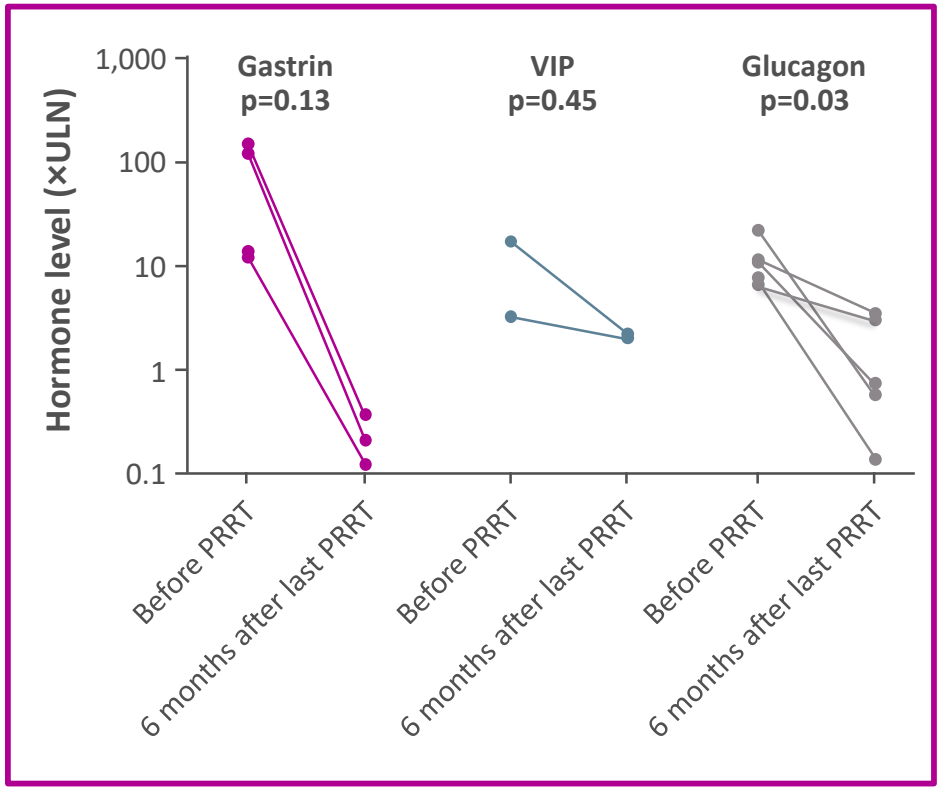
High Symptomatic and radiological response

- Symptomatic response: 71%
- Radiological response: 59%

Increased Quality of Life (EORTC QLQ-C30)

- Symptomatic response often persists despite radiological progression

	All (n=34)	Insulinoma (n=14)	Gastrinoma (n=7)	VIPoma (n=5)	Glucagonoma (n=8)
Symptomatic response N (%)	17 (70.8)	6 (66.7)	2 (66.7)	4 (80.0)	5 (71.4)



EORTC, European Organisation for Research and Treatment of Cancer; Lu177, lutetium 177; panNET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; ULN, upper limit of normal; VIP, vasoactive intestinal peptide

Zandee W, et al. J Clin Endocrinol Metab. 2019;104:1336-44

TREATMENT: TARGETED THERAPY

Everolimus

- Associated with reduced tumour proliferation in NET[1]
- Improves PFS in patients with advanced panNET
  - 11 months with everolimus vs 4.6 months with placebo[1]
- Insulinoma: control recurrent hypoglycaemia[2]
- Potential reduction of glucagon and gastrin,[3] associated with new onset diabetes[4]

Sunitinib

- Improved PFS, OS, and ORR as compared with placebo among patients with advanced panNET. May be due to anti-apoptotic and antiproliferative effect[5]
- VIPoma: reduction of diarrhoea in case reports[6]
- Insulinoma: sunitinib might increase insulin secretion (increase of hypoglycaemias?)[7]

ORR, objective response rate; OS, overall survival; (pan)NET, (pancreatic)neuroendocrine tumour; PFS, progression free survival

1. Yao J, et al. N Engl J Med. 2011;364:514-23; 2. Bernard V, et al. Eur J Endocrinol. 2013;168:665-74; 3. Pavel M, et al. Pancreas 2017;46:751-7; 4. Vergès B, et al. Diabetes Research and Clinical Practice 2015; 110: 101-108; 5. Raymond E, et al. N Engl J Med. 2011;364:501-13; 6. de Mestier L, et al. Eur J Endocrinol. 2015;172:K1-3; 7. Thijs AM, et al. Br J Clin Pharmacol. 2016 2015;81:768-72

LIVER-DIRECTED THERAPIES

- Severity of symptoms is often associated with tumour burden
- Reduction of liver tumour burden could potentially reduce symptoms (from mass and hormonal hypersecretion)
- Liver metastases can be resected or treated by (*depending on local availability*):
  - Transarterial bland embolisation
  - Radioembolisation/selective internal radiation therapy (SIRT)
  - radiofrequency ablation (RFA)
  - microwave and cryoablation
  - high-intensity focused ultrasound (HIFU)
  - Laser ablation
  - brachytherapy and irreversible electroporation (IRE)

Frilling A, et al. Lancet Oncol. 2014;15(1):p.e8-21; Lee SY, et al. In J Hepatol 2012;2012:146590. doi:10.1155/2012/146590;
de Herder W, et al. https://www.ncbi.nlm.nih.gov/books/NBK278981/Accessed 27-Nov-20

CONCLUSIONS

- Functioning panNETs are rare: adequate symptomatic control is essential

Treatment options

- Reduce secretion: somatostatin analog often first line
- Combine with specific symptomatic treatment (e.g diet for insulinoma)
- Second-line: PRRT is especially effective for symptom control

panNET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy

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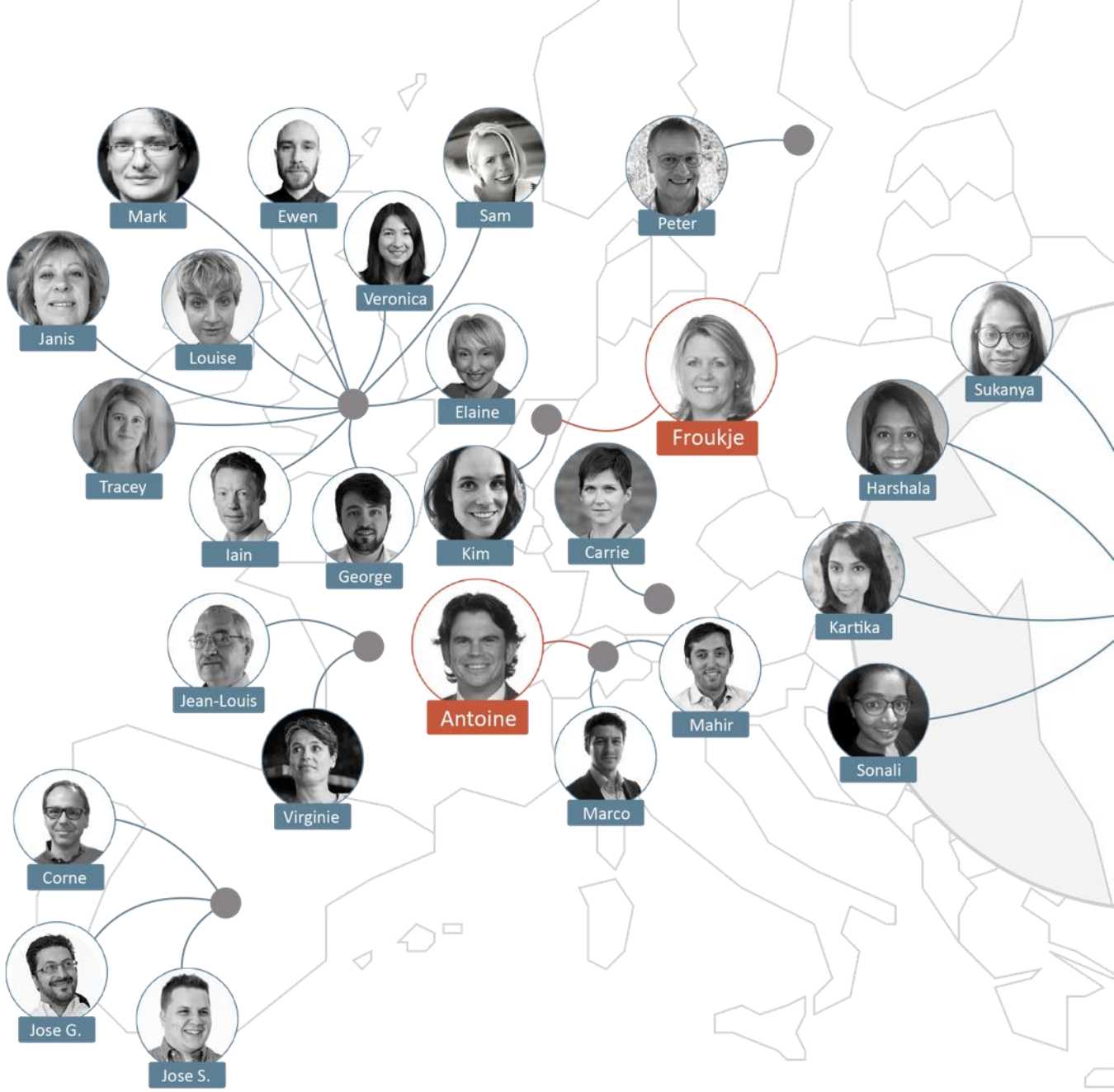

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