Multidisciplinary insights for Cushing's disease: Individualized medical management of patients for whom surgery is not an option or not curative

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Expert panel

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Mrs Sandra Ramsburg
Pituitary Nurse Specialist, Pituitary Center, Johns Hopkins Division of Endocrinology, Diabetes and Metabolism, Baltimore, MD, USA

Dr Timothy Smith
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Ms Sharmyn McGraw
Patient, 23 years in remission with Cushing's disease, Orange County, CA, USA

Discussion 1

Challenges in the management of Cushing's disease: What is the goal of medical therapy?

Dr Timothy Smith
Neurosurgeon–scientist

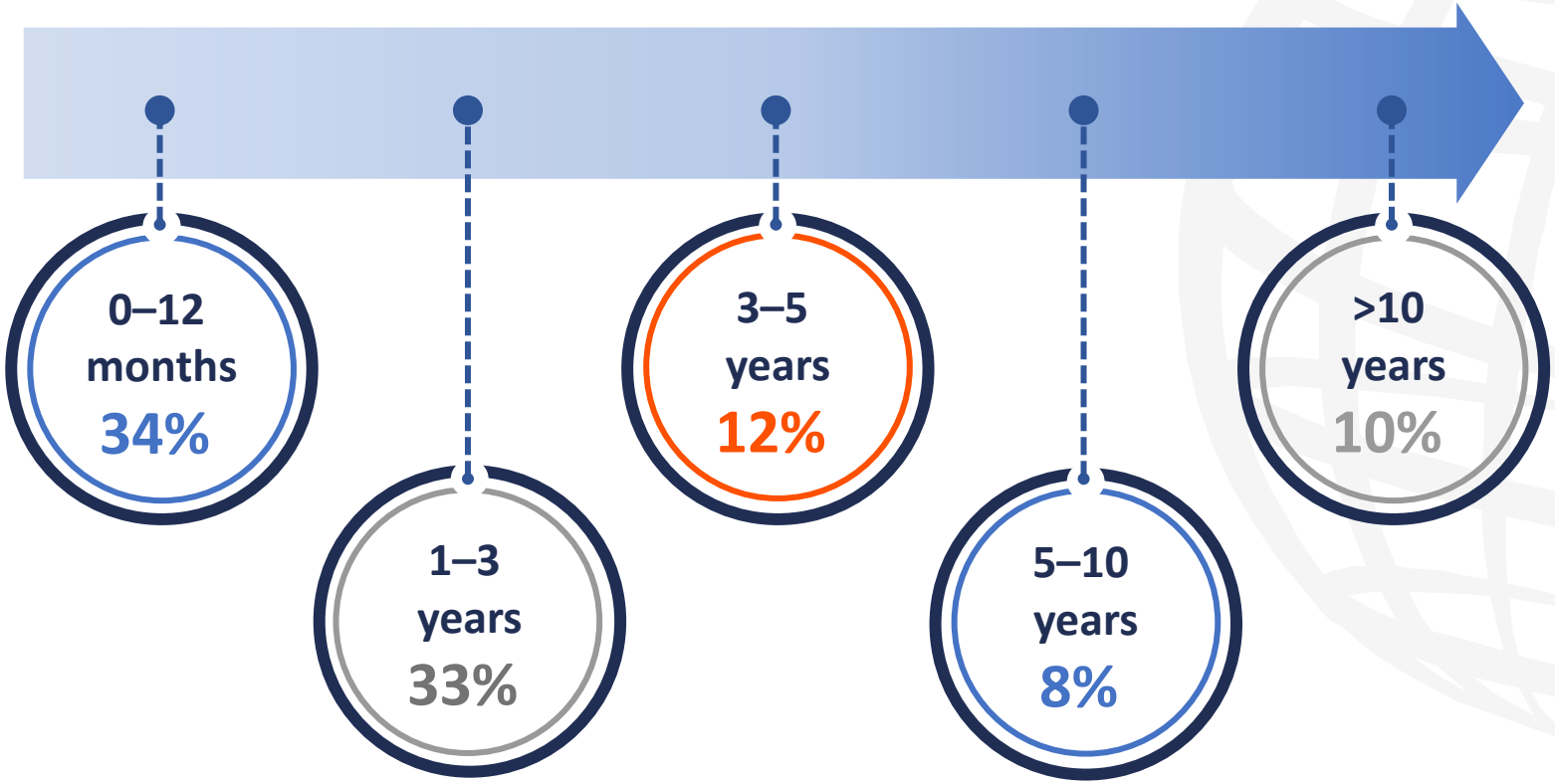
Dr Laurence Katznelson
Endocrinologist

Ms Sharmyn McGraw
Patient, 23 years in remission with Cushing's disease

Cushing's disease: Prevalence and diagnostic delay

Estimated global prevalence[1*]

Time from first symptoms to diagnosis (N=320)[2†]



*Based on a systematic review and meta-analysis of studies on Cushing's disease epidemiology from inception until 30 November 2020. Number denotes pooled prevalence.
Global Cushing's disease prevalence ranged from 0.3 (95% CI 0.0–2.4) to 6.2 (95% CI 4.0–9.6) cases per 100,000 people; †Reported by patients in the World Association for Pituitary Organisations 2019 global survey. Three per cent of participants reported "Unknown" for time from first symptoms to diagnosis.

1. Giuffrida G, et al. *J Endocrinol Invest.* 2022;45:1235–46; 2. Valassi E, et al. *Endocr Connect*. 2022;11:e220027.

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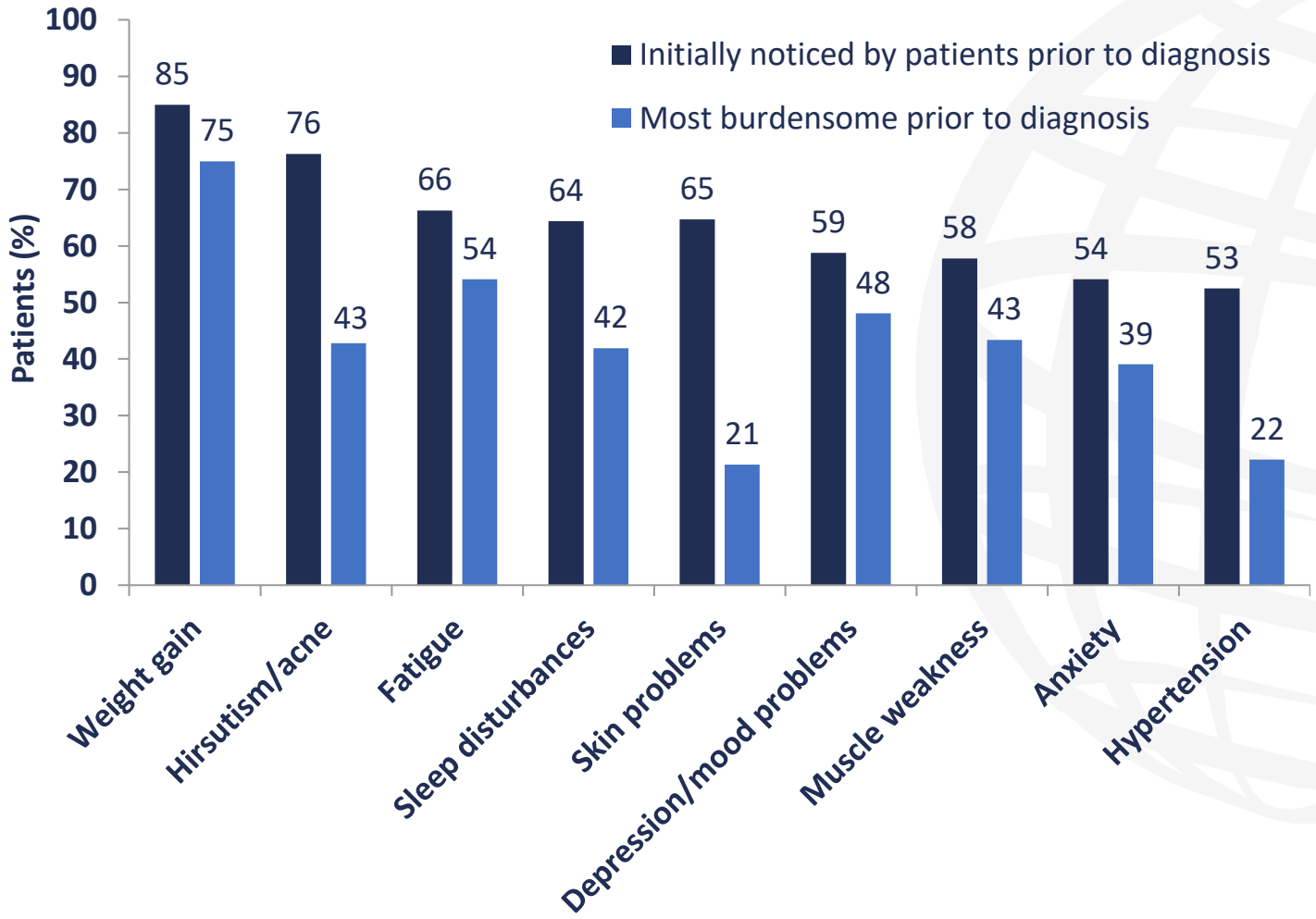
Cushing's disease: Symptoms and comorbidities

Associated comorbidities[1,2]

- Hypertension
- Hyperlipidaemia
- IGT, T2D
- Hypercoagulability
- Osteoporosis
- CVD
- Neuropsychiatric
- Infections
- Hyperandrogenism
- Obesity

Proportion of patients reporting symptoms (N=320)[3*]

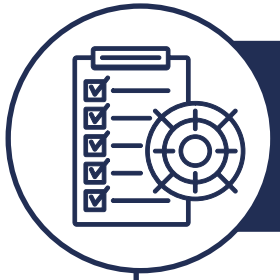


*World Association for Pituitary Organisations 2019 global survey.
CVD, cardiovascular disease; IGT, impaired glucose tolerance; T2D, type 2 diabetes.
1. Savas M, et al. *J Clin Endocrinol Metab*. 2022;107:3162–74; 2. Scoffings K, et al. *Br J Gen Pract*. 2022;72:399–401; 3. Valassi E, et al. *Endocr Connect*. 2022;11:e220027.

Treatment goals for management of patients with Cushing's disease

Primary goal

Normalize cortisol concentrations*[1]



Additional goals

- Address clinical features[2,3]
- Treat comorbidities[2,3]
- Improve quality of life[3]
- Achieve long-term remission without recurrence[2]

*Or cortisol action if using mifepristone.

1. Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021;9:847–75; 2. Aulinas A, Webb SM. In: Tamagno G, Gahete MD. Pituitary Adenomas: The European Neuroendocrine Association's Young Researcher Committee Overview. Springer Nature, 2022;1–335; 3. Nieman LK, et al. *J Clin Endocrinol Metab.* 2015;100:2807–31.

Discussion 2

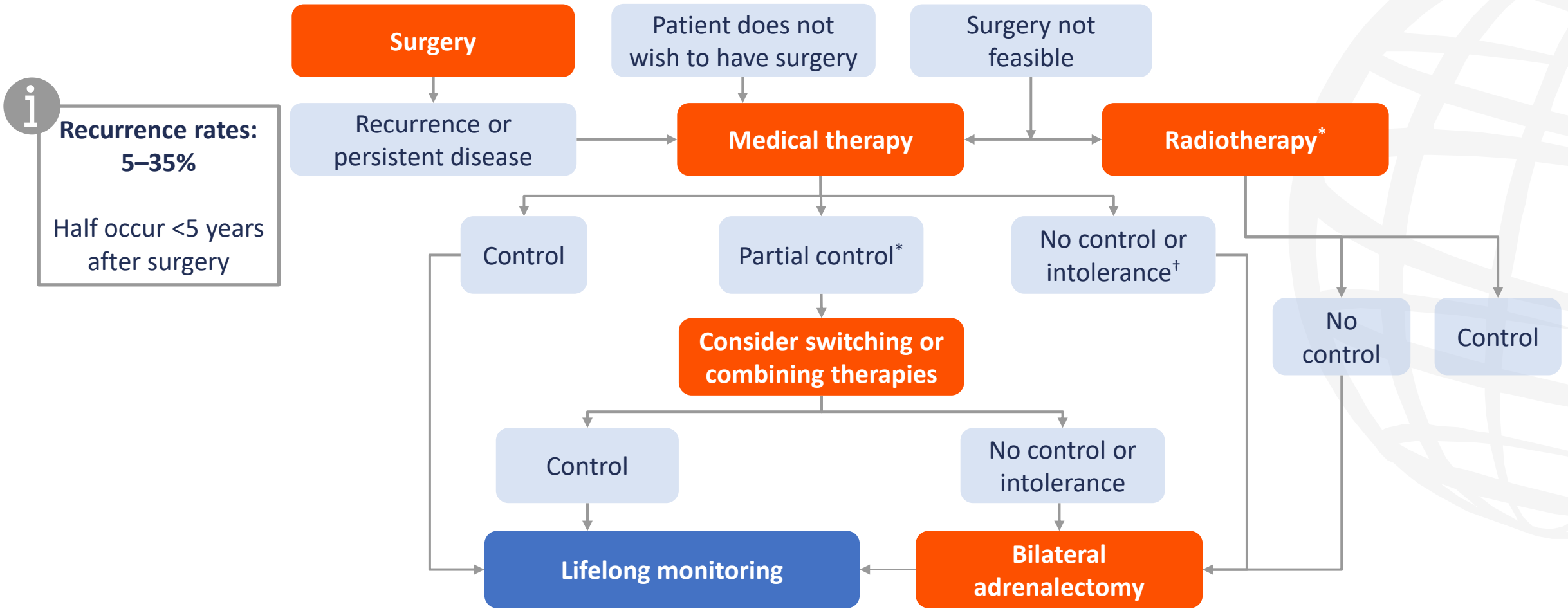
Medical therapies for the treatment of Cushing's disease: What are the clinical considerations?

Dr Laurence Katznelson
Endocrinologist

Dr Timothy Smith
Neurosurgeon–scientist

Mrs Sandra Ramsburg
Pituitary Nurse Specialist

Overview of medical treatment and monitoring pathways for patients with Cushing's disease



*Lifelong monitoring for hypopituitarism and secondary neoplasia in the radiation field required; †On maximum tolerated dose.

Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021;9:847–75.

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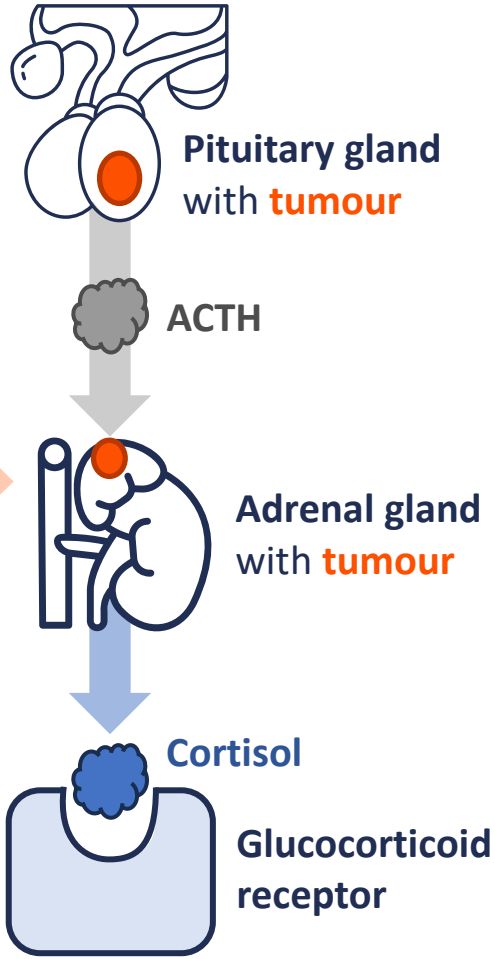
FDA-approved medical therapies for Cushing's disease: Mechanisms of action



Adrenal steroidogenesis inhibitors[1,2]

- Osilodrostat
- Levoketoconazole
- Mitotane

Somatostatin receptor ligand[2]

- Pasireotide

Glucocorticoid receptor blocker[2]

- Mifepristone

ACTH, adrenocorticotropic hormone; FDA, United States Food and Drug Administration; LAR, long-acting release.

1. Favero V, et al. *Int J Mol Sci*. 2021;22:11521; 2. Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021;9:847–75.

FDA-approved medical therapies for Cushing's disease

	Mifepristone[1,2]	Mitotane[1,2]	Levoketoconazole[1–3]	Osilodrostat[1,2,4,5]	Pasireotide[1,2]
Indication	Hyperglycaemia secondary to endogenous CS, when surgery is not an option or not curative	Inoperable, functional or non-functional, adrenal cortical carcinoma	Cushing's disease, when pituitary surgery is not an option or has not been curative		
Administration	Oral, q.d.	Oral, t.i.d. or q.i.d.	Oral, b.i.d.	Oral, b.i.d.	Subcutaneous, b.i.d. or intramuscular, q4w†
Efficacy*, % patients	Significant improvement in glycaemia (~60) and BP	UFC normalization: 80	mUFC normalization overall: 58	mUFC normalization: 75–81	UFC normalization: 15–40
Adverse effects (≥15% [mitotane only] or ≥30% of patients)	Nausea, fatigue, headache, hypokalaemia, endometrial hypertrophy; black box warning for termination of pregnancy	Anorexia, nausea, vomiting and diarrhoea, depression, dizziness or vertigo, rash; black box warning for adrenal crisis in the setting of shock or severe trauma	Nausea/vomiting, erythema, haemorrhage/contusion, fatigue, headache, abdominal pain/dyspepsia; black box warning for hepatotoxicity and QT prolongation	Adrenal insufficiency, fatigue, nausea, headache	Diarrhoea, cholelithiasis, hyperglycaemia, diabetes mellitus, nausea‡

*Data cannot be directly compared due to differences in trial design and study populations; †Pasireotide: subcutaneous b.i.d. administration. Pasireotide LAR: intramuscular q4w; ‡Nausea ≥30% of patients applies to pasireotide only. b.i.d., twice daily; BP, blood pressure; CS, Cushing's syndrome; FDA, United States Food and Drug Administration; LAR, long-acting release; mUFC, mean UFC; q4w, every 4 weeks; q.d., once daily; q.i.d., four times daily; t.i.d., three times daily; UFC, urinary-free cortisol.

1. Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021;9:847–75; 2. FDA. Individual drug PIs. Available at: www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed 25 January 2023); 3. Pivonello R, et al. *Pituitary*. 2022;25:911–26; 4. Fleseriu M, et al. *Eur J Endocrinol*. 2022;187:531–41; 5. Fleseriu M, et al. *Pituitary*. 2022;25:959–70.

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Discussion 3

Strategies to optimize patient outcomes in Cushing's disease: Individualized therapy and the role of the MDT

Dr Laurence Katznelson
Endocrinologist

Dr Timothy Smith
Neurosurgeon–scientist

Mrs Sandra Ramsburg
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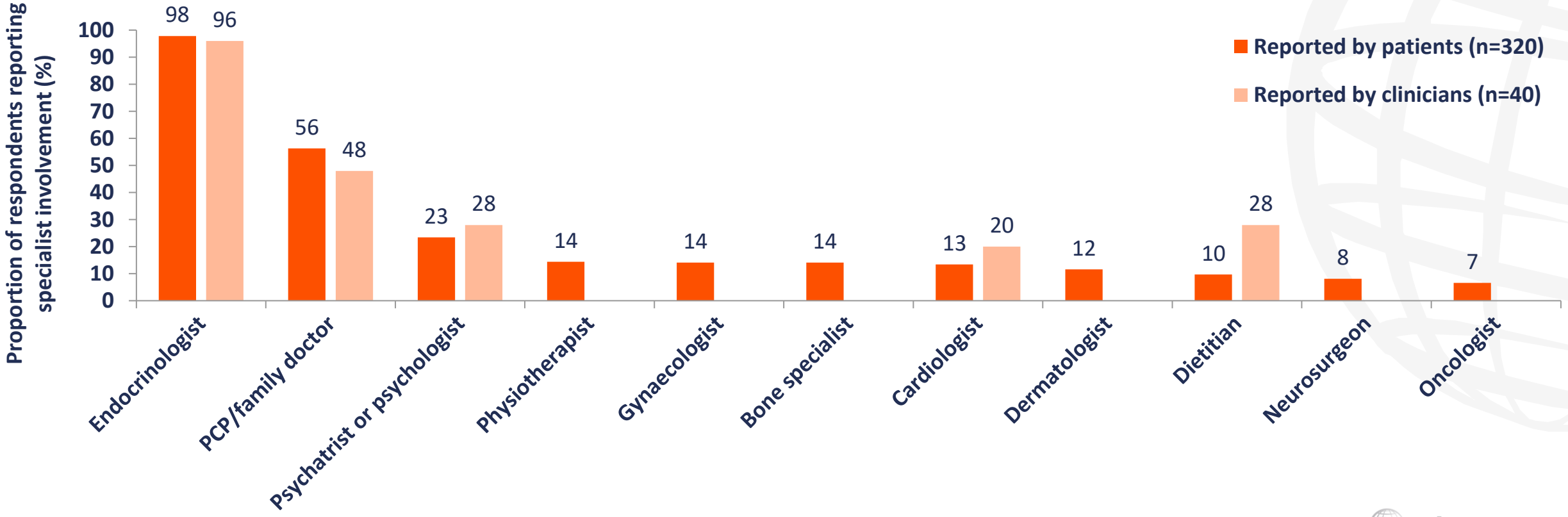
Patient, 23 years in remission with Cushing's disease

MDT care for patients with Cushing's disease

Many specialists are involved in the care of patients with Cushing's disease….

…although some differences in the perception of specialist involvement between patients and clinicians may indicate a deficiency in effective MDT management

Specialists involved in CD management as reported in the World Association for Pituitary Organisations 2019 global survey



CD, Cushing's disease; MDT, multidisciplinary team; PCP, primary care physician.

Valassi E, et al. *Endocr Connect*. 2022;11:e220027.

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