Hypercortisolism

	1. ACTH-secreting pituitary adenoma (corticotroph adenoma)	2. Ectopic ACTH production	3. Primary adrenal adenoma	4. Adrenal carcinoma	5. Primary adrenal hyperplasia	6. Multinodular bilateral adrenal hyperplasia
Other names or indications from the name	Cushing disease	-	-	-	Primary: the problem in adrenal gland not in pituitary Hyperplasia: it not a tumor, just proliferation of cells independent of ACTH	Micronodular: the nodules are small bilateral adrenal hyperplasia: both adrenal glands enlarged
Prevalence	the most common cause of endogenous hypercorticolism (60%)	5-10% of endogenous Cushing syndrome cases	10-20% of ACTH-independent cases	5-7% of ACTH-independent cases (less common than adenoma)	Rare	-
Most common affected	Women, young adults	Men (one of the underlying causes is lung cancer which is common in men), middle age	-	-	-	-
Functioning	✅	✅	✅	✅	✅	✅
Size of neoplasm/ tumor / gland	Microadenoma / small size	-	Smaller than adrenal carcinoma	Very large size of adrenal glands (larger than the adenoma)	nodules are larger than 1 cm	nodules are smaller than 1 cm (in radiology and naked eye we don't see nodules)
ACTH dependence	✅	✅	❌	❌	❌	❌
Level of ACTH	High	High	Low ACTH level (negative feedback on pituitary)	Low ACTH level (negative feedback on pituitary)	Low	Low
Causes or mutations	-	1. Small cell carcinoma of the lung (most common) / 2. Carcinoids tumor (benign tumor of neuroendocrine gland in the GI system) / 3. Medullary carcinoma of thyroid / 4. Pancreatic neuroendocrine tumors	PRKAR1A (protein kinase mutations) genetic mutation	Genetic mutations in: 1. activation of beta-catenin (CTNNB1) / 2. inactivation of TP53 / 3. MEN1 / 4. PRKAR1A (protein kinase mutations)	1. Familial disease(family history; more than one in the same family): inherited mutation in the tumor suppressor gene: armadillo repeat containing 5 (ARMC5)(this mutation is inherited) 2. Sporadic disease: 50% show ARNC5 mutation(here the mutation acquired later on), others show ectopic production of G-protein coupled hormone receptors (similar action of ACTH)(ACTH is suppressed, but the cells secrete protein mimic ACTH action) 3. Syndromic disease(rarest one) McCune Albright syndrome(multiple mutations and diseases), germline activating mutation in GNAS, produces excessive cAMP(potent oncogene ; cause proliferation of cells) → multisystemic disease(this patients have multiple endocrine diseases not only the adrenal)	Two variants are primary pigmented nodular adrenocortical disease (we see the adrenal gland by naked eye dark brown in color instead of yellow) and Carney complex (multisystemic disease of endocrine and non-endocrine neoplasms) (multiple tumors ,one of them is proliferation in adrenal gland). Two variants both harbor mutation in cAMP-dependent protein kinase (PRKAR1A gene), producing excessive cAMP (all of these mutations lead to excess cortisol secretion)
Special cases	In rare cases, corticotroph hyperplasia rather than adenoma (excessive CRH secretion from hypothalamic tumor) (high CRH secretion cause corticotroph hyperplasia and hyperfunction)	In some cases, ectopic production of CRH(instead of ACTH secretion they secrete CRH) (will lead to same effect)	-	-	-	-
Hyperplasia of adrenal gland	✅ bilateral nodular hyperplasia(enlargement of both adrenal glands because adrenal gland depend on ACTH)	✅ Bilateral nodular hyperplasia	❌ The other adrenal gland is atrophic (due to low ACTH levels)	❌ The other adrenal gland is atrophic	✅ Shows bilateral adrenal cortical hyperplasia	✅ Shows bilateral adrenal cortical hyperplasia
Notes	-	Pathologic changes is less prominent than pituitary cause, secondary to poor prognosis of accompanied cancer (they die from cancer instead of complications of hypercortisolism)	-	Produces very high level of cortisol results in very prominent symptoms	Syndromic disease is the rarest	

Don't forget: the most common cause of ACTH independent hypercortisolism is exogenous intake of cortisols

In pituitary adenoma, the pituitary gland is large and we have high ACTH levels ,while in primary adrenal hyperplasia the pituitary gland is normal and ACTH levels is low.