

## VALIDITY STATEMENT FOR SALIVA TESTING

Saliva testing of steroid hormones has been documented in the scientific literature for almost 30 years and is routinely used in scientific research settings and as standard textbook material for students of endocrinology and internal medicine (Williams Textbook of Endocrinology)

There is, in fact, a substantial volume of published clinical and scientific research strongly supporting saliva testing of steroid hormones (estradiol, progesterone, testosterone, DHEA, cortisol) as superior in many cases to serum testing for determination of hormone imbalance. (See enclosures). This research redresses any misconception that saliva hormone testing methods lack validity.

Dr. Peter Ellison of Harvard University, in conjunction with the World Health organization, has used salivary hormone testing to compare cross-cultural estrogen levels between women living in Western vs. non-industrialized countries. WHO approved this modality in the 1990s when it was found to be an accurate, convenient, noninvasive measurement of free hormone levels.

Additionally, as you know, there is an enormous amount of literature on hormones based on serum/plasma assays. Steroids in saliva reflect the portion of circulating hormones in the bloodstream that are unbound (free or bioavailable) by serum binding proteins and enter tissues throughout the body. The salivary hormone values, therefore, reflect the biologically active (the unbound) portion available to target cells. Blood hormone assays reflect both bound and free forms and do not provide information about the bioavailable fraction of hormone, which can vary depending on the level of blood hormone binding proteins.

Significantly, many insurance companies cover the cost of saliva testing because it has been shown to be as accurate as blood testing and more cost effective. Although serum/hormone is the traditional matrix tested for steroid hormones, saliva testing is proven to be as effective as serum testing. The difference between effectiveness of these matrices does not establish or support the superiority of one measure over the other.

In short, the weight of evidence clearly validates salivary testing as a well established technique used not only in this country but also worldwide to measure steroid hormone levels in both men and women.



## Vital Health Pharmacist

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## The Science of Saliva Testing

Estrogens (estrone, estradiol and estriol), progesterone, testosterone, DHEA-S and cortisol are routinely measured in saliva at ZRT. Why saliva? Steroid hormones in the bloodstream are mostly (95-99%) bound to carrier proteins (hormone-binding globulins, albumin), and in this form they are unavailable to target tissues. Only the unbound fraction freely diffuses into tissues, including the salivary gland. Hormone levels in saliva therefore represent the quantity of the hormone that is currently available to target tissues and actively exerting specific effects on the body. Because of this, salivary hormone levels often relate to specific symptoms of hormone excesses or deficiencies. Research at ZRT has demonstrated clear correlations between salivary hormone levels and reported symptoms. The rationale for and clinical utility of saliva testing is well documented <sup>1-13</sup>.

The very small concentrations of salivary hormones (only 1 – 5% of the total hormone levels that include protein-bound hormone found in serum) necessitate extremely sensitive assay methods. This is a particular issue for estrogens, which are present in very minute quantities in saliva, especially in older populations such as postmenopausal women. ZRT is unique as the only commercial laboratory using extracted saliva testing for estrogens. Extraction removes contaminants that interfere with the assay and concentrates the sample, significantly improving assay sensitivity compared to the "direct" assay methods available commercially <sup>14</sup>. In fact, poor correlations between serum tests and non-extraction salivary estradiol assays have unfortunately led to some skepticism about saliva testing. Also, because of the extremely sensitive assays, it is important to avoid blood contamination of saliva as a result of oral injury, therefore toothbrushing must be avoided before collecting saliva for testing <sup>15</sup>. Saliva testing may also not be appropriate for sublingual hormone users unless samples are obtained at least 36 hours after the last dose. Blood spot testing is a preferred option for these patients.

Conversely, when some hormones, notably progesterone, are administered topically, saliva levels can rise higher than serum levels<sup>16,17</sup>. This is because progesterone is carried to target tissues including the salivary glands, where there is rapid uptake and release of the hormone into tissues and saliva, leaving very little hormone in the venous blood returning from the tissues <sup>18</sup>. Tissue levels of progesterone have been found to be very high after topical progesterone use <sup>19-21</sup>, and a biological response can be demonstrated, e.g., the reduction of endometrial cell proliferation caused by estrogen therapy <sup>22</sup>. We have recently published a clinical study showing saliva levels of progesterone increased 10-fold while capillary blood spot levels increased 100-fold compared to levels in venous whole blood and venous serum following application of 80 mg progesterone cream or gel<sup>23</sup>. This has led us to conclude that when hormones are delivered through the skin or oral or vaginal mucosa, conventional serum hormone tests grossly underestimate hormone delivery to tissues. In contrast, hormone levels in saliva or capillary blood spot better represent tissue hormone uptake.

DHEA-S, the sulfated storage form of DHEA, is measured rather than DHEA because its levels are more stable (DHEA has a much shorter half life in blood) and at ZRT it has been found to correlate very well with reported clinical symptoms. However, as a conjugated hormone that does not diffuse into saliva as rapidly as the unconjugated hormones measured in ZRT's other hormone assays, its passage into saliva is flow rate dependent <sup>12</sup> and therefore flow stimulants such as gum chewing are not advised prior to saliva collection.

Research at ZRT shows good correlations between salivary hormone levels and dosages of hormones given exogenously. Saliva testing is therefore a good option for monitoring hormone therapy and adjusting dosages if necessary.

