**INTEGRATIVE APPROACHES TO BREAST CANCER: EVALUATION & MANAGEMENT**

### RISK FACTORS
- FAMILY HISTORY AND INHERITABLE GENE MUTATIONS BRCA1/2
- MTHF C677T HOMOZYGOUS SNP
- INCREASED BREAST DENSITY
- IONIZING RADIATION [mammography?]
- OBESITY
- ALCOHOL AND OTHER TOXINS heavy metals
- VITAMIN D DEFICIENCY <20ng/mL 80% more likely than >60ng/mL
- ROTATING NIGHT SHIFT + many other risk factors contribute

### SIGNS & SYMPTOMS
- CHANGE IN HOW THE BREAST OR NIPPLE FEELS lump, thickening
- CHANGE IN BREAST OR NIPPLE APPEARANCE OR COLOR
- INCREASE IN SIZE OR CHANGE IN SHAPE OF THE BREAST
- DISCHARGE FROM THE NIPPLE clear or bloody
- GENERAL PAIN IN OR ANY PART OF THE BREAST
- LUMPS OR NODES FELT ON OR INSIDE THE BREASTS
- ITCHING OR IRRITATED BREASTS
- PEELING OR FLAKING OF THE NIPPLE SKIN

### BREAST CANCER DIAGNOSTICS
- BREAST SELF-EXAMINATION [go to algorithm text #1]
- CA 15.3, 27.29, 19.9, CA125, CEA [serial monitoring]
- IVYGENE DNA methylation pattern, non-specific screening test
- Circulating Tumor Cells target <5 [Biocept, OncoDNA, QUEST]
- NAGALASE [Health Diagnostics and Research Institute]
- THERMOGRAPHY [baseline then 3mo, if normal then annually]
- ULTRASOUND best choice for women <40yoa or dense breasts
- MRI WITH CONTRAST
- MAMMOGRAPHY [consider harms, 3-D not recommended]
- BIOPSY for tumor molecular profile
  - O, ER, PR, HER2 status +/-
  - MAMMAPRINT 70-gene Bcara recurrence assay
    - Low risk = 10% recurrence in 10 years, no tx
    - High risk = 29% recurrence in 10 years, no tx
  - ONCOTYPE DX likelihood recurrence & benefit from Tx
    - >50yoa, low recurrence risk <25 = no chemo
    - <50yoa, low recurrence risk <15 = no chemo
  - DCIS <39, low risk = no radiation
  - Ki-67 low risk <10%, borderline 10-20%, high risk >20%
- CARIS MOLECULAR INTELLIGENCE
- WEISSENTHAL CANCER GROUP
- OncoDNA – [OncoSelect- tumor biomarkers through blood]
- BIOCEPTS [CTCs and tumor biomarkers through blood analysis]

### HOST “TERRAIN” LABORATORY EVALUATION
- COMPLETE BLOOD COUNT NLR <5, optimal <2, PLR <150
- COMPREHENSIVE METABOLIC PANEL fasting, optimal FAR <7.1
- 25 OH VITAMIN D >50ng/mL <100ng/mL
- RBC ZINC [or serum zinc] target high normal
- RBC Selenium 120-300mcg/L
- CERULOPLASMIN [or serum copper] target low normal
- HIGH SENSITIVITY C-REACTIVE PROTEIN [HS-CRP] <1.0mg/L
- INTERLEUKIN-6 <7pg/mL, TNFa <8.1pg/mL, IL-18 <3.9pg/mL
- FASTING INSULIN <10iu/mL, optimal <5iu/mL
- HgA1c <5.7%, optimal <5.2%
- SEX HORMONE BINDING GLOBULIN reference range, inverse
- TOTAL AND FREE TESTOSTERONE [early morning] high normal
- ESTRONE SULFATE <15ng/dL
- ESTRONE, estrone sulfate-to-estradiol ratio <2 post-menopausal
- PROLACTIN reference range
- LEPTIN <15ng/mL
- ADIPONECTIN
- THYROID EVAL – TSH, Free T3, Total T3, Free T4, Total T4, TPO/TG
- DHEA +/- CORTISOL AM/PM high normal reference range
- GALECTIN 3 <18ng/mL
- FIBRINOGEN <375mg/dL
- D-DIMER <0.4mg/L
- HOMOCYSTEINE [HCY] 7-8umol/L
- INSULIN LIKE GROWTH FACTOR 1 [IGF-1] +/- IGFBP-3
- HER2neu QUANTITATIVE reference range <14
- LACTATE DEHYDROGENASE
- Ph FIRST MORNING COLLECTION >7

### LIFESTYLE PRESCRIPTION
- OPTIMAL BODY MASS INDEX 18.5-27.5
- EXERCISE 5 DAYS/WEEK minimum 75 minutes vigorous exercise or 150 minutes moderate exercise per week
- MINIMIZE ALCOHOL 1 drinks/day or less
- MINIMIZE STRESS through exercise, meditation, prayer
- MINIMIZE ESTROGENIC INFLUENCES from environment
- MINIMIZE CHEMICAL EXPOSURES smoking, cleaning products
- MINIMIZE MEAT chose hormone & antibiotic free
- MINIMIZE DAIRY
- MINIMIZE HIGH COPPER FOODS
- AVOID UNHEALTHY TRANS-FATS
- AVOID PROCESSED FOODS, sugar and artificial sweeteners

### NUTRICEUTICAL AND BOTANICAL MEDICINE PRESCRIPTION dosages based on individual profile
- MULTI-VITAMIN without copper and iron [XYMOGENE, PURE]
- ZINC 40-100mg daily in divided doses based on blood levels
- MODIFIED CITRUS PECTIN 5MG TID if galectin-3 >18ng/mL
- VITAMIN D3 5000IU-10,000IU DAILY [+ or 1000IU/30lb
- FLAXSEED 2-3sp in smoothie daily + chia seeds
- BROMEALIN or LUMBROKINASE based on fibrinogen, d-dimer
- CHRYSIN based on estrone sulfate >15ng/dL post-menopausal
- DI-INDOLE METHANE [DIM]
- CALCIUM D-GLUCARATE 500mg TID
- PROBIOTIC [Therbiotic complete, KLAIRE]
- PSP 50-200mg @bed, titrate until dreaming, reduce if too vivid

- ORGANIC FOODS, non-GMO, locally grown
- ANTI-INFLAMMATORY DIET, Mediterranean + olive oil
- HIGH INTAKE VEGETABLES emphasis green & cruciferous
- HIGH INTAKE ONIONS, GARLIC, SCALLIONS
- HIGH INTAKE OF MUSHROOMS esp. white button
- HIGH INTAKE FIBER flaxseed, chia seed, legumes, nuts ~9gm/d
- HIGH INTAKE HERBS AND SPICES turmeric, ginger, rosemary etc...
- MODEST INTAKE LOW GLYCEMIC FRUITS emphasis on berries
- LIMITED INTAKE WHOLE GRAINS
- IODINE FROM FISH, SEAWEED, BLADDERWACK [300-500mcg]
- SOY FOODS miso, tempeh, natto / [NF] tofu, soybean milk
- OVERNIGHT FAST OF 13hrs and do not eat within 2hrs of bedtime

- COMPLETE OMEGA ESSENTIALS [N] 3-5 tablets divide doses
- BOTANICAL TREASURES [N] 9-18 tablets divided doses
- IMMUCAR II [N] 9-18 tablets divided doses
- INFLAMAWAY [N] 9-12 tablets divided doses
- CELL GUARDIAN [N] 3-9 tablets in divided doses
- IG SENSITIZER [N] 1-2 tablets with each meal if insulin elevated
- TURMERIC 3-6 grams daily in divided doses
- TUMOR OINTMENT SALVE applied to site of tumor [not blk salve]
- ARTEMIS PLUS [N] special instructions – cytotoxic botanicals
- PHYTOCYTO [N] special instructions – cytotoxic botanicals
- OTHER: Magnesium, IP6, melatonin, black cumin seed oil
COMPLETE BLOOD COUNT

The neutrophil-to-lymphocyte ratio can be prognostic. To obtain the ratio, divide absolute or relative neutrophil levels by lymphocyte levels. Optimal levels are <2. A ratio >5 predicts advanced disease or progression. This is typically observed as rising neutrophil and diminishing lymphocyte levels. Similarly, the platelet-to-lymphocyte ratio offers prognostic information and is useful for monitoring purposes on serial studies. It is obtained by dividing platelets (in thousands) by lymphocyte count (absolute cells/μL). Values >150 are associated with more advanced disease or progression. Rising platelet levels warrants concern. Falling lymphocytes may indicate cancer is taking control of the immune system or may be seen following radiation therapy. Monitor also for indications of anemia which can complicate cancer but use caution with iron supplementation when cancer is present. Utilize anti-inflammatory botanicals like Turmeric, Botanical Treasures [N] and InflamAway [N] when NLR is elevated.

COMPREHENSIVE METABOLIC PANEL

Evaluate for evidence of insulin resistance, pre-diabetes or diabetes. Monitor kidney enzymes, electrolytes, proteins and liver enzymes. Low levels of proteins are seen in advanced disease. Utilize Beyond Whey [N] for whey-based protein and immune support. If patient is cachexic with low protein consider additional support Amino Max [N], Botanabal [N]. Fibrinogen-to-albumin ratio (FAR) was defined as the concentration ratio of fibrinogen (mg/dL) to albumin (mg/dL) multiplied by 100. (fibrinogen in mg/dL/albumin in mg/dL)×100. The optimal cutoff was <7.1. High levels of alkaline phosphatase with normal ALT/AST (and GGT) should be followed-up with bone specific alkaline phosphatase to evaluate metastatic risk. Bone metastasis can also be evaluated by urinary N-terminal telopeptide (NTX). Elevated levels indicate increased bone turnover which may be seen in metastatic disease and osteoporosis.

25 OH VITAMIN D

Women with 25 OH vitamin D <20ng/mL were found to be 80% more likely to develop breast cancer than women >60ng/mL. Titrate to target dose based on follow-up testing at 2month. Recommend Vitamin D3 [1000IU/30bl] with simultaneous vitamin K dosing - DAK [N].

RBC OR SERUM ZINC

Target upper normal range and use to competitively inhibit copper levels if copper or ceruloplasmin outside of lower 1/3 reference range.

CEHEROS OR SERUM COPPER

Copper promotes new blood vessel formation (angiogenesis) which provide a blood supply to the developing tumor. Upregulation of ceruloplasmin/copper occurs as a tumor takes over the environment. Utilize zinc to inhibit copper absorption and titrate to effective dose based on lab values, typical dosage 40-100mg/day. Molybdenum glycinate can be used to chelate copper if additional copper lowering support is needed but do not use if uric acid elevated. Minimize or avoid copper containing foods and multivitamins. Consume extra zinc when eating foods containing copper such as avocado and nuts. Filter water if copper pipes are source of drinking water. Ceruloplasmin/copper levels should be maintained at low-normal ranges. Target a zinc-to-copper ratio of 3:1 (serum values).

HIGH SENSITIVITY-CRP

Non-specific marker of inflammation (interleukin-6). Utilize anti-inflammatory protocols (Mediterranean diet, low glycemic index foods) and botanicals like Botanical Treasures [N], InflamAway [N] (Parthenolide can cause reversible tasteful taste loss — reduce dose or discontinue if severe).

FASTING INSULIN

Elevated insulin levels promote inflammation and tumor development. Utilize exercise, low-glycemic index diet and insulin sensitizing botanicals like IG-sensitizer [N]. Berberine, Chromium picolinate, vanadon, Chinese cinnamon bark. Use of a vegetarian diet (short-term, 1-4 weeks) may reset insulin receptors and is recommended in stubborn cases. Intermittent fasting or fast mimicking diet may be useful tools if additional therapeutic options related to blood sugar are needed.

SEX HORMONE DISCUSSION & PROLACTIN

Higher levels of SHBG may indicated less available “free” circulating sex hormones which may be advantageous but high levels may also be an indication of estrogen dominance. Estrone sulfate is the storage form of aggressive estrogens and is a better marker than estradiol in cancer assessment. In post-menopausal women >15ng/dL use natural aromatase inhibitors chrysin, zinc. Prolactin elevations promote tumor growth and increases bone metastasis. Antipsychotics may increase prolactin levels. Vitex and sage/ursoic acid may help lower prolactin elevations.

LEPTIN & ADIPONECTIN

The higher the leptin-to-adiponectin ratio the higher the risk for breast cancer. Leptin is a pro-inflammatory adipokine associated with insulin resistance and increased risk of breast cancer and mortality. Adiponectin is an anti-inflammatory adipokine. Leptin lowering effects can be achieved with vitamin D, fish oils, alpha lipoic acid and conjugated linoleic acid. Adiponectin can be increased with vitamin D, Vitamin E, Fish oils, Fiber and extended release niacin. 25gm flaxseed/day lowers leptin and increases adiponectin.

THYROID EVALUATION

Target mid or lower 1/3rd of normal reference range for T3, T4. Avoid hypothyroid or high reference ranges (+) of thyroid. Increased metabolic rate induced by high thyroid hormones may increase cancer metabolism and promote progression. Levothyroxine use increases risk for breast cancer. Consider Reverse T3 assessment and evaluation of ratios to more sensitive determination of hypothyroidism at a cellular level. RT3 optimal 11-18ng/dL, FT3:FT4 ratio >.33, TT3:RT3 >6, FT3:RT3 >20 (Luby/IFM).

GALECTIN-3

In involved in proliferation, apoptosis, inflammation, fibrosis, progression and metastasis. Optimal range <18ng/mL. If elevated, utilize modified citrus pectin [PectalSol-C ecoNugenic or Designs for Health] taken in doses of 5 grams TID.

FIBRINOGEN & D-DIMER

Elevations have been found with cancer development, progression, tumor angiogenesis and metastatic spread. High-fibrinogen inhibits the immune system from targeting cancer cells by acting as a shield. Target <375mg/mL - use supplements like bromelain 500mg taken every 8 hours on an empty stomach, policosanol 10mg BID, Lumbrokinase 2 tablets TID 30min before food for 3-6 weeks, fish oils (Complete Omega Essentials) 4-grams/day, turmeric 2-grams/day, garlic. D-dimer can also be used to assess hypercoagulation potential and elevations can be influenced by above noted natural medicines and is a more serious indicator of active thrombosis.

HOMOCYSTEINE

Elevated levels are associated with some cancers when methionine-dependent malignant cells are unable to convert homocysteine to methionine. Elevations of HCY are indicative of methylation impairments. Eliminate red meat and coffee while level HCY remains elevated on retesting consider methylating supplement support such as Homocysteine Supreme – Designs for Health (avoid or utilize caution during active chemotherapy treatments) and weigh risk of B12/folate use in cancer treatment.

INSULIN LIKE GROWTH FACTOR-1 [IGF-1]

Elevated levels have been found in breast cancer although studies are mixed. Target low normal reference range by reducing or eliminating dairy, high-glycemic index foods and by providing S-alpha reductase inhibitors like saw palmetto and zinc. Option Serenoa Supreme [N].

HER2 QUANTITATIVE

HER2 positive cancer support with fish oils, olives, Chrysin, EGCG, DIM, vitamin D, watercress, cruciferous vegetables, high fiber, curcumin.

LACTATE DEHYROGENASE

Elevations outside of reference range are associated with lactic acidosis or may be a biomarker of cancer progression. Utilize alkalinizing strategies (see below)

FIRST MORNING URINE PH

Target 7.0-7.5 and utilize alkalinizing diet, vegetarian diet, baking soda ½ - 1 tsp BID on empty stomach, Tri-salts, Digest Mend [N] and Bragg's organic apple cider vinegar 1tsp diluted in water TID. Tagamet 800mg at bedtime when acidosis is refractory to natural alkalinizing strategies.
1 – Monthly self-breast examination (SBE) has not shown benefit in reducing breast cancer mortality compared with no screening and may lead to more biopsies (1.8% vs 1.0%) and more diagnosis of benign breast disease. Nonetheless, in my opinion, breast awareness should be encouraged. Patient handout for how to perform SBE can be downloaded from: http://maurerfoundation.org/wp-content/uploads/maurer_sbe_flier_v4.pdf

2 – Continue monthly self-breast examination. Clinical breast examination (CBE) is a breast exam performed by a healthcare provider. Randomized controlled trials of CBE are on-going but one study suggests CBE may show equivalent benefit with mammography. 3-D mammography (digital breast tomosynthesis) benefit over 2-D mammography is lacking but may have an advantage in women with dense breasts, <50yoa and pre or perimenopausal women. Potential harms are substantial and include higher radiation dosage than 2-D mammography and breast compression. There is no absolute consensus for when screening (by mammography) should be performed. The American Cancer Society recommends women 40-44yoa start annual screening with mammography if they chose, women 45-54yoa annually, women 55yoa and older every two years and only screen women with greater than 10-year life expectancy. The US Preventative Services Task Force 2016 recommends women make an individual choice whether to screen between ages 40-49, women 50-74 every two years and no benefit for women 75yoa and older. Recommendations are for asymptomatic women without prior breast cancer diagnosis or other high-risk breast lesions.

3 – If the self-breast examination is abnormal then proceed to ultrasound examination. Thermography may be used to establish baseline or to compare to prior studies, but thermography is not reliable as the sole diagnostic imaging method. Mammography should be performed cautiously with consideration of poor sensitivity, harms of false positive and risks of ionizing radiation and breast compression. If positive for BRCA1 or BRCA2 (DNA repair genes) the harms of ionizing radiation are increased, and ultrasound or MRI with contrast are preferred imaging methods.

4 – If follow-up imaging after abnormal self-breast examination is normal consider repeat testing at 1-3 months or proceed to #5 (blood screening) if clinical impression is high risk despite normal imaging. If imaging results are normal on follow-up evaluation and clinical impression is low risk (no blood marker testing performed), then reset algorithm to #1 (monthly self-breast examinations)

5 – Serum breast cancer biomarkers CA 15.3, CA 27.29, CA 19.9, CA 125, CEAb. IvyGene provides a quantitative marker of tumor burden and is validated for breast, colon, liver and lung cancer based on DNA methylation patterns of circulating tumor DNA (may be useful with cancers of other origin but has only been validated to date for those listed). Quantify Circulating Tumor Cells [OncoDNA, Biocept or QUEST] to establish baseline for serial monitoring – desired range <5. Nagalase is a protein made by cancer cells and viruses that blocks production of GcMAF which may inhibit immune activation against cancer. Although this test is less favored (my opinion) it measures Nagalase and may be used for tracking of anti-cancer regime therapeutic benefit [http://gcmaf.tsimthmd.com/book/chapter/52/]. Performed by US lab Health Diagnostics and Research Institute.

6 – MRI with contrast has greater sensitivity than mammography without ionizing radiation. Harms include higher risk of false positive and contrast agent (can assess gadolinium burden on Doctor’s Data urine heavy metal profile). MRI preferred if patient has breast implants, is a known BRCA1/2 carrier or is considered high-risk based on family history or prior chest radiation (cancer treatments).

7 – Advantages of tumor profiling through blood (vs tissue biopsy) include ease of access and ability to monitor and perform serially and thus compare the clinically actionable cancer biomarkers (tumor characteristics in terms of genomics and proteomics) that may occur over time and through the course of treatment. The advantage of analysis through tissue biopsy (vs liquid blood biopsy) is the ability to perform additional prognostic tests such as MammaPrint, Oncotype DX, Ki67 and others. If tissue biopsy is to be performed, consider the following: 1) If premenopausal then perform biopsy at menses when estrogen levels are low, 2) if post-menopausal deplete estrogen reserves (for >3 weeks before biopsy) with prescription aromatase inhibitor or natural aromatase inhibition such as Chrysins, inositol hexaphosphate (IP6), zinc, vitamin D3, Vitamin B6 as pyridoxine-5-phosphate (PSP), 3) reduce inflammation by using Cox-2 inhibitor (Celebrex or Turmeric) and Beta-2 adrenergic receptor blocking agent (propranolol or rauwolfia) to dampen and subsequent cytokine response. Also, do not perform biopsy (or surgery) when patient is unusually stressed.

8 – After molecular profile obtained proceed to #11

9 – Establish hormone receptor status (estrogen and progesterone receptor positive or negative) and human epidermal growth factor 2 receptor status. MammaPrint can be utilized to predict recurrence risk as low or high in patients with early-stage breast cancers that are stage I or stage II, invasive, smaller than 5cm and either estrogen receptor positive or negative. “Low Risk” MammaPrint means that a patient has on average a 10% chance of recurrence within 10 years without any additional adjuvant treatment (hormonal or chemotherapy) after surgery (lumpectomy). “High Risk” means that a patient has a 29% chance of recurrence within 10 years without any additional adjuvant treatment. Oncotype DX is the most validated test for prognostic and predictive value. Oncotype DX recurrence score <18 is low risk, 18-30 intermediate risk and >31 high risk. Ki-67 is a cancer antigen found in growing or rapidly dividing cells. Measures of Ki-67 expression in cancer cells from tissue biopsy help predict aggressiveness of the cancer. A Ki-67 <10% is low risk, 10-20% intermediate risk and >20% is high risk. Cancers with a high Ki-67 and higher proliferative rate are more sensitive to chemotherapy treatments.

10 – High risk breast cancer patients should seek additional tumor genomic and proteomic information through Caris Life Sciences Molecular Intelligence, Weisenthal Cancer Group Personalized Cytometric Tumor Profiling (tests cancer cell survival vs various chemotherapy agents), OncoDNA (liquid +/- tissue biopsy) or Biocests (liquid biopsy).

11 – Hormone receptor (estrogen +/- progesterone) positive and HER2 negative without lymph node involvement. Proceed to #12.

12 – Low risk pre-menopausal women that are HR positive, HER2 negative and node negative may consider prescription aromatase inhibition +/- Lupron or Zoladex (ovarian suppression of estrogen). If oncologist recommends Tamoxifen, then insist on testing for CYP2D6 status. If SNP variation found on genetic evaluation, DO NOT use Tamoxifen. If Tamoxifen is selected, induce CYP2D6 to enhance conversion of Tamoxifen (pro-drug) to active drug by using hypericum (Titrante hypericum to photosensitization then reduce – 300-1800mg/day) and green tea. New recommendations for Tamoxifen based on 2018 studies are low dose (5mg) for only 3 years.

Low risk post-menopausal women that are HR positive, HER2 negative and node negative breast cancer may consider prescription aromatase inhibitor (Letrozole, Exemastin or Anastrozole) if estrone sulfate >15pg/dl or natural aromatase inhibition (Chrysins) if <15pg/dl [note: Letrozole may lead to upregulation of HER2 and MAPK signaling proteins]. Initial daily dosing of Rx aromatase inhibition can be reduced to 3x/week after 1 month and later may consider reducing to 2x/week monitoring symptoms, estrone sulfate and supporting bone and heart health. All women should be given opportunity for terrain evaluation and appropriate natural terrain supportive therapies and natural or Rx blood thinners if d-dimer and fibrinogen elevations not otherwise explained.

13, 14 – HR negative, HER2 positive patients should be given option for Herceptin +/- Docetaxel + Perjeta + Rtx aromatase inhibition + natural terrain supportive measures. 15 – HR negative, HER2 negative patients should complete advanced tumor profiling + natural terrain supportive measures.

ADDENDUM: If biopsy, lumpectomy or mastectomy is planned, at least 3 weeks prior begin anti-estrogen therapy, anti-inflammatory therapy (Celebrex/Turmeric) and anti-B2 adrenergic receptor therapy (propranolol/rauwolfa) +/- metformin. Local anesthesia preferred over general and may block stress response of surgery. Breast conserving surgery preferred to mastectomy in early cancers. If surgery performed, intraoperative NSAID use improved outcomes. Avoid breast implants. If utilized, chemotherapy before radiation. [No chemo benefit in HR positive, HER2 negative, low Ki67, low Oncotype DX]. If chemo used, fast 24 hours before and after therapy. Do not perform radiation >70yoa and when used, pre-load and apply radiosensitizing and radioprotective botanicals and nutraceuticals (red yeast rice, vitamin E as mixed tocopherols, ashwagandha(?), turmeric, melatonin, zinc +). If chemotherapy is used: prefer taxanes (Paclitaxel/Taxol and Docetaxel/Taxotere) over Adriamycin/Doxycyclin. Zometa (bisphosphonate) can be added to aromatase inhibitor to prevent bone loss or Denosumab twice/year (monoclonal aby treatment for bone loss). Monitor bone health/loss with N-telopeptide urine test. New advances in treatment: Focused microwave hyperthermaphy from Medifocus or Jason Williams, Golf Shores, AL.

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