Skin and Subcutaneous Tumors
Just like in small animals, skin and subcutaneous tumors are the most commonly diagnosed neoplasms in horses. These tumors have both benign and malignant variants. The main treatment option is of course surgical resection. Alternate treatment options will also be discussed.

Melanocytic Tumors
Melanocytic tumors are seen in virtually all species. In large animals, they are most common in horses (up to 15% of all skin tumors); specifically, grey horses. Their behavior in horses varies from indolent to malignant with wide spread systemic involvement.

Signalment: Melanomas are seen in both grey and non-grey horses but more commonly grey. There is no age or sex predilection. Some believe that malignant versions are more common in non-grey horses but there is no substantiative proof to this thought. The incidence of melanocytic tumors increases with age up to 80% (for grey horses) by age 15.

Etiology: In most horses, the origin of melanocytic tumors is NOT thought to be related to sun exposure. In grey horses, the gene associated with “graying” leads to increased risk of tumor formation. This gene is referred to as STX17 and copy-number expansion of the gene has been linked to the grey horse color and increased expression of melanocytic genes. Furthermore, there are specific SUBSETS of grey horses that have mutations in the agouti gene (gene responsible for bay colored horses) that further increase risk for tumor formation and may contribute to the generalized melanomatosis presentation. These mutations are inherited in an autosomal dominant fashion and can be tested for.

Key learning note: Melanocytic tumors are most commonly seen in grey horses. Specific genetic mutations increase the risk of melanoma formation.

Behavior: More than 90% of melanocytic tumors are benign at initial presentation (nevus or dermal melanomas), but up to 2/3 can progress to malignancy. These tumors can be divided into four distinct clinical syndromes in horses:

1. Melanocytic nevus are solitary superficial masses seen in both grey and non-grey. Surgical excision is curative. These are benign as name suggests.
2. Dermal melanoma is typically seen only in grey horses and can occur singly or with multiple lesions. Incidence is extremely high in grey horses (numbers as high as 50% noted). They are locally invasive and can spread to visceral sites.
3. Dermal melanomatosis this is the more aggressive version of the melanoma and is only clinically different than above tumor. Multiple cutaneous tumors
and visceral involvement is noted. Only noted in grey horses. Essentially, this is the malignant version of dermal melanoma in grey horses.

4. Anaplastic malignant melanoma can occur in any coat color horse and are highly aggressive. They typically consist of solitary skin lesions with visceral involvement. Histologically they differ from dermal melanomas by being anaplastic. Clinically they are highly metastatic.

Key learning note: There are four variants of melanocytic tumors in horses. Two are benign and two are considered malignant.

Histopathology: Nevus are well-differentiated tumors that show minimal infiltrative behavior. Dermal melanomas and melanomatosis are identical histologically and vary only in clinical behavior. The histopathology of dermal melanomas and melanomatosis are like benign human melanocytic tumors and exhibit few if any histologic criteria of malignancy.

Clinical signs: Most equine melanocytic tumors arise in the skin of the perineal region, ventral tail, and external genitalia. The oral site is also relatively common after the previously mentioned sites. The vast number of melanocytic tumors physically appear as darkly-pigmented masses or thickened dermal regions. For internal lesions, a variety of non-specific signs could be expected but most commonly include colic signs.

Diagnosis: The diagnosis of equine melanocytic tumors is routine. Signalment (grey horse) is obviously informative along with physical tumor appearance that is usually characteristic and darkly-pigmented. In questionable cases, cytology and/or biopsy can be useful.

Treatment: Surgical resection is the treatment of choice and curative for nevi or dermal melanomas if complete margins are achieved. Surgery should be performed early in disease course when margins can be curative. However, surgery is still considered the core of therapy in patients with advanced tumors. Debulking procedures or marginal resections, even if the wound bed is left to heal by contraction, are often effective at palliating symptoms associated with the disease. In patients with loco-regionally advanced tumors that aren’t amenable to resection then other modalities can be considered. Coarsely-fractionated radiation protocols have been used but are limited due to cost of therapy and access to the modality. Intralesional chemotherapy has proven moderately effective, especially for smaller tumors, and typically involves the use of platinum-based drugs. Hyperthermia, or the use of microwave heating, combined with intraliesional platinum-drugs has proven quite efficacious for localized lesions, evener larger tumors. A similar approach called electrochemotherapy utilizes localized electric currents in combination with intraliesional chemotherapy to improve clinical response rates. Both hyperthermia and electrochemotherapy can be considered for clinical cases not amenable to surgical resection; however, neither supply any systemic protective or therapeutic effects. Systemic therapies have been limited to immunotherapies including both non-specific generalized stimulants and targeted agents. Non-specific immunotherapies such as bacteria cell wall extracts (BCG) and immunocytokines have
been described. Specific immunotherapies include the use of a human tyrosinase xenogenic DNA vaccine (i.e. the canine melanoma vaccine), whole tumor-based vaccines, along with other tumor-specific-antigen therapies. A final drug that is routinely considered in patients with wide-spread disease is cimetidine. Cimetidine thought to have immunomodulatory properties and is often prescribed. True clinical response rate is unknown with some suggesting no defined activity while others suggest up to 50-90% regression in one report. The dosage that has been described for such indications is 1.6 mg/kg PO q24hr.

Prognosis: For solitary lesions and localized benign variants treated surgically, the prognosis is good to excellent. Horses with wide-spread disease or with non-resectable lesions will inevitably succumb to the disease and thus the prognosis is guarded to grave for these presentations.

Future: Studies are currently underway aimed at further understanding the genetic basis of this tumor in grey horses and identifying new immunotherapeutic treatment options.

Key learning note: Treatment typically involves surgical resection. Immunotherapy likely is effective in some animals; although, it is likely best used in early cases.

Equine Sarcoid
Sarcoids are locally aggressive, fibroblastic skin tumors that are the most common skin tumor in horses comprising ~90% of skin tumors (~20% of all tumors).

Signalment: There is no apparent age or sex predilection (but see below) but most cases are seen in horses <4 yrs. A well-described predilection has been noted for thoroughbreds and geldings; although this seems anecdotal at best.

Etiology: A direct causative etiology has not been identified; however, there is strong evidence to suggest that bovine papillomavirus (types 1 and 2) is associated with tumor formation. Specifically, it is believed that the E5, E6, and E7 viral proteins contribute to the transformation of equine fibroblasts. Further, increasing viral load has been associated with increased clinical aggressiveness of equine sarcoids. Bovine papillomavirus has also been associated with other disease processes including canker. The mode of transmission for this virus amongst horses has not been determined; however, it is believed that there is a wide-spread occurrence of latent infection amongst equids. Studies have even demonstrated a possible heritable basis of sarcoid disease amongst horses with a presumed polygenic inheritance pattern.

Key learning note: Sarcoids are the most common skin tumor in horses. Etiology of sarcoids is thought to be viral (BPV), transmission mode is unknown. Quantification of viral load may be useful for determining clinical aggressiveness of disease.

Behavior: Sarcoid tumors can appear as benign wart-like lesions that can spontaneously regress to large ulcerated fibrous growths. These growths can be found anywhere on the body but are more common on the head, lips, neck, around the eyes, legs; rarely found on
the back. They can also be seen at the sites of previous trauma. There are six clinically recognized forms based on their appearance and behavior: Occult, nodular, verrucose (warty), fibroblastic (proud-flesh), mixed (warty and proud-flesh), and malevolent. The fibroblastic, mixed, and malevolent types are more aggressive; histologically these can be diagnosed as soft tissue sarcomas when there is no obvious skin involvement of the tumor. The occult, nodular and verrucose forms are considered lower-grade and have up to a 32% incidence of spontaneous resolution. The lower-grade variants do not metastasize and show minimal local invasion, however, the higher-grade tumors are locally invasive and can result in metastatic spread (i.e. those “called” soft tissue sarcomas).

Key learning note: Sarcoids have a wide range of clinical behavior, from benign to aggressive. Local recurrence is common for facial tumors. Spontaneous resolution may occur.

Histopathology: All sarcoid tumors contain both epidermal and dermal components. The dermal portion of the tumor classically involves a mesenchymal proliferation. The more aggressive variants may invade the deeper tissues and thus have substantive mesenchymal components. The more aggressive variants with little skin involvement and significant mesenchymal components are usually diagnosed as soft tissue sarcomas (e.g. fibrosarcoma, etc). The epidermal components of sarcoids include epidermal hyperplasia, hyperkeratosis, rete peg and 'picket fence' formation while the dermal components consist of invasive fibroblasts and connective tissue components. Again, the more aggressive variants will have extensive dermal components; in some cases, the dermal cells will exhibit sufficient criteria of malignancy and thus warrant the diagnosis of sarcoma.

Diagnosis: The diagnosis of equine sarcoid is typically made based on clinical appearance and location; however, histopathology is required to differentiate between other benign and malignant tumors. Further biopsy is required to differentiate from other proliferative conditions including granulation tissue formation. As noted above, determination of viral load may also be helpful in determining clinical aggressiveness.

Treatment: The treatment of choice for all solid tumors including sarcoids is surgical resection. Complete resection is curative for low-grade tumors but some of the more common locations are associated with a high incidence of local recurrence (periocular and facial). Extensive tumors, high-grade tumors, and tumors with high viral loads are also associated with a high-incidence of local recurrence. Additional therapies are thus typically required in these select locations and in patients with aggressive variants. Other treatment options that have been described include laser therapy, radiation therapy, cryotherapy, intralesional chemotherapy, electrochemotherapy, thermochemotherapy (hyperthermia), and immunotherapy. Laser excision is frequently preferred to sharp surgery and may be associated with improved rates of local control. Radiation therapy typically involves the use of brachytherapy modalities and coarse-fractionated protocols (i.e. single high-dose protocols). Using these approaches, success rates reach 80-100%. Cryotherapy has been used as an adjuvant therapy to surgery to sterilize residual disease
after surgical resection. This modality is typically limited to small disease fields with minimal deep tissue invasion. Intralesional chemotherapy is an approach that is often used in lieu of surgical resection and can be applied to both early and more advanced tumors. The drug of choice is clearly cisplatin; although, bleomycin, 5-fluorouracil, and carboplatin have shown activity. Drug protocols for the more commonly used agents are as follows:

1. **5-Fluorouracil**: Can be injected intralesionally at doses of 1-3 ml per tumor site (pending size of tumor). Epinephrine is typically adding to the injection at ratio of 1 part : 10 parts 5-FU. Can also be mixed with sterile sesame seed oil (1:1) immediately prior to usage then injected. Generally successful for resolution of lesions. Maximum systemic dosage ~750 mg.

2. **Cisplatin**: This has been used in a similar fashion to 5-FU. However, it is currently only available in an aqueous form (at 1 mg/ml). Previously, it was available in a lyophilized form that could be diluted to desired concentration. Technique and dilutions are same as 5-FU. Maximum systemic dosage is ~100 mg.

3. **Carboplatin**: Commonly used in place of cisplatin due to availability of a generic form. The platinum drugs have much higher response rates than 5-FU. Generally injected at a dosage of 1 ml/cm³ of tumor (all drugs use this ratio of drug to tumor) while staying below maximum systemic dosage. Maximum systemic dosage ~1000 mg for average horse.

Electrochemotherapy involves the use of localized electrical currents to improve chemotherapy drug uptake by the tumor. This tends to improve tumor response rates but is limited to smaller superficial tumors. Hyperthermia has also been used to treat macroscopic tumors with variable success. This approach is also limited to superficial tumors but does not require anesthesia to administer and allows for the successful treatment of relatively larger tumors. Numerous immunotherapeutic approaches have been described including:

1. **Intralesional BCG**: In this approach, bacterial extracts are injected directly into the tumor tissue. This is associated with ~60-70% success rates. Both modified live and killed cell wall preparations have been used. Successes are typically seen only with the minimally invasive, superficial lesions. Anecdotally, the peri-ocular variants have been reported to be more responsive.

2. **Autogenous vaccines**: In this approach, tumor tissue is harvested from the affected horse and used to create an endogenous vaccine. This approach has been widely described and routinely used; however, studies have failed to demonstrate a significant benefit.

3. **Non-specific immunostimulants**: Novel agents such as topically applied Imiquimod have shown response rates as high as 70-80%; although this is most likely to work on the superficial, minimally invasive lesions.

**Prognosis**: The prognosis is generally good to excellent for the clear majority of cases due to the indolent nature of the disease. Small, low-grade tumors can be treated successfully with surgical resection. More advanced tumors or tumors in select anatomic locations can be more difficult to treat. The periocular and head/neck lesions are often more difficult to treat due to anatomic constraints and thus warranted a more guarded prognosis. Recurrent
lesions, large tumors, or tumors with high-viral loads tend to be more aggressive and thus are associated with a guarded prognosis.

A simplified treatment protocol for equine sarcoids is presented below:

1. **Primary treatment**: Surgical resection when feasible while considering adjuvant treatment to the tumor base if incompletely excised. Adjuvant treatment options include cryotherapy, radiation therapy, electrochemotherapy, thermochemotherapy, or immune-modulators.

2. **Secondary treatment**: In cases where primary surgical resection is not feasible, options include:
   - **Radiation therapy**: Coarsely-fractionated protocols involving single or few doses of radiation therapy are associated with high response rates. Typically, however, it is combined with at least a marginal resection of the tumor and is thus considered an adjuvant option (see above).
   - **Intralesional cytotoxic chemotherapy** with either 5-FU (maximum dosage should be less than ~750 mg/horse with appropriate amount determined individually) or cisplatin (~1 mg/cm³ of tumor with maximum dosage <100 mg/horse to avoid nephrotoxicity)
   - **Topical Imiquimod**: This medication comes in packets of cream that is applied topically MWF (thin layer due to cost) to tolerance (it will cause inflammation so you apply it until the lesion is red and inflamed then stop and allow the inflammation to resolve. Continue with this approach pending response to therapy. This approach is limited to superficial lesions or combined with surgical debulking.
   - **Topical fluoride/zinc containing compounds**: Anecdotally, there is some experience with the use of “Tooth-paste” applied topically to sarcoids (used in similar fashion to imiquimod above). Tumors have been noted to “shrink” in response to administration. True response rate is unknown.
   - **Topical caustic agents**: The most common topical agent utilizes a compound called blood-root salve and is essentially caustic to epidermal tissue.
   - **Intralesional immunotherapy** such as BCG or other immune stimulants. The current marketed version of BCG is called Regressin and is composed of a purified bacteria cell wall extract. Injections are given weekly until regression. Expect a profound inflammatory response following injection. Response rates are unknown.

**Key learning note**: Sarcoids are typically treated with surgical resection (+/- adjuvant therapy to tumor base). Success rates with virtually all modalities are high with early lesions. Large and invasive lesions behave like soft tissue sarcomas and can be quite difficult to treat.

Squamous Cell Carcinoma of the Horse
Two different variants will be discussed: those that involve the skin or mucocutaneous junctions and those that involve the external genitalia.

Cutaneous Squamous Cell Carcinoma (SCC)
These tumors occur primarily around the eye and at mucocutaneous junctions and are considered the second most prevalent skin tumor found in horses. These areas of course are the non-pigmented tissues and thus more susceptible to solar-induced damage.

Signalment: This malignancy is most common in middle to older age horses and there is no gender predilection. Lightly pigmented horses and lightly pigmented regions of the body are more commonly affected. Several breeds of horses are at increased risk and include Appaloosas, Clydesdales, shires, and Belgians.

Etiology: The most important etiology is thought to be solar-induced epidermal damage; however, a strong viral etiology (equine papillomavirus) has also been proposed (at least for urogenital variants). These tumors can also be seen in previously traumatized skin (burned etc) and thus trauma induction (non-solar related) is also thought to be etiologic.

Behavior: These tumors are considered locally invasive; however, the solar-induced variants rarely metastasize. Local recurrence following marginal resection is very common and nearly expected in clinical patients. The clinical signs that are seen in affected patients include the presence of ulcerative or proliferative lesions, conjunctivitis for eyelid lesions, and other signs pending disease site. Due to the actinic (solar) nature of this disease, it is often multifocal in any given horse.

Diagnosis: The diagnosis of cutaneous SCC can be made based on location of the lesion in non-pigmented regions, breed, appearance of lesion, and histopathology or cytology in questionable cases.

Treatment: Surgical resection and/or cryotherapy are the most common treatment approaches used in affected horses. Tumors that are considered non-resectable lesions can be treated with intralesional chemotherapy as previously described for sarcoids. Electrochemotherapy and thermochemotherapy (hyperthermia) can also be considered as described previously for non-resectable lesions. Chemotherapy options that are typically used either alone or in combination include 5-Fluorouracil, cisplatin, carboplatin, and bleomycin. There is some support that the oral non-steroidal Piroxicam may also have efficacy (see below).

Prevention: Solar exposure has been linked to the development of these

Large ulcerative preputial SCC in a horse
tumors and thus reducing solar exposure can be beneficial. Options include fly-sheets and masks, topical ointments to prone areas, and night-time turnout.

**Key learning note:** Squamous cell carcinomas are relatively common solar-induced tumors. Local therapy is typically curative but should be followed with preventative therapy.

**Urogenital SCC**

This tumor is most commonly seen on the penis or sheath of intact or geldings and is considered the most common malignancy to affect these regions.

**Signalment:** This tumor shows a clear gender predilection and appears to be most common in stallions or geldings. It is also more commonly seen in the same breeds at increased risk for cutaneous SCC. The disease is most common in middle-aged to older horses.

**Etiology:** The etiology of these tumors is thought to be like the cutaneous forms, solar exposure or perhaps irritation from smegma is thought to play a role. There is also some initial evidence suggesting the involvement of a novel equine papilloma virus in tumor formation.

**Behavior:** The clinical signs seen in affected patients depend on tumor extent and location; however, they include a foul odor, bleeding masses, difficulty urinating, and failure to drop during urination. Early tumors or pre-cancerous lesions result in focal tumors. Larger tumors and more aggressive variants have aggressive local growth and moderate rates of metastasis (up to 15%). The lesions may be ulcerative or proliferative and can affect any portion of the penis but typically the non-pigmented portion, the glans, and the inner sheath. As the tumors progress, metastasis may be seen to the draining lymph nodes and local recurrence is common following marginal resection. Another concept that is important when considering these tumors is called “field cancerization”. “Field cancerization” implies that an entire field of tissue has been exposed to a cancer-causing stimulus and thus is placed at heightened risk of tumor formation. The result is that multiple independent lesions develop over time within the at-risk field. In other words, if they get one lesion they are at risk for developing others in the future which will also require therapy.

**Diagnosis:** The diagnosis of urogenital Squamous cell carcinoma can be made based on location of the lesion, breed, appearance of lesion, and histopathology or cytology in questionable cases.

**Treatment:** Surgical resection is the most common therapeutic approach; however, high recurrence rates are expected with all but the most superficial lesions. Radical surgical resection, while less commonly pursued, is associated with markedly higher rates of local recurrence.
control. Adjuvant therapies can be added to surgical resection with the goal of improving local control. Cryotherapy is one such example of an adjuvant therapy which can also be used as a sole modality for early lesions. Effective deep-freezing along with multiple freeze-thaw cycles are critical for success with this approach. Intrallesional chemotherapy either as a sole agent or in combination with electrochemotherapy can also be quite effective but is typically limited to focal solid lesions. Ulcerative lesions, either single or multifocal, can be treated with the topical chemotherapy 5-fluorouracil. This will cause a profound local inflammatory response and thus application must be closely monitored for patient tolerance. The drug is generally applied 1-3 times weekly to every other week pending patient tolerance until complete resolution. The oral non-steroidal Piroxicam has also been reported to have activity against these lesions and may play a role in preventing future lesions. Studies have demonstrated that the piroxicam molecular target (cox-2 enzyme) is significantly overexpressed within these equine tumors. Targeting this enzyme may thus provide clinical benefit. The drug is dosed at 0.1-0.3 mg/kg/day while watching out for ulcerative disorders. In theory, other non-steroidals may exhibit similar activity.

Prognosis: The prognosis is typically good for early lesions but local recurrence is common. Adjuvant therapies (topical 5-FU, cryotherapy, piroxicam) may help lower the incidence of local recurrence. Concerning features such as multifocal tumors, large tumor burden, metastatic disease, high mitotic index or vascular invasion on biopsy may denote a more guarded prognosis.

Key learning note: Unlike cutaneous SCC, the local recurrence rate of these tumors is quite high and their local behavior is more aggressive. Treatment should occur early in disease and should be aggressive. Most common treatments include surgery, laser ablation, and cryotherapy. Topical 5-Fluorouracil can be useful. Horses that develop this tumor are at risk for local recurrence and/or new tumors. Early and aggressive therapy along with the use of agents such as piroxicam may prevent further lesions. Finally, some initial evidence suggests a role for a novel equine papilloma virus in the etiology of these tumors.